Functional Specialization of ON and OFF Cortical Pathways for Global-Slow and Local-Fast Vision

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SUMMARY

Visual information is processed in the cortex by ON and OFF pathways that respond to light and dark stimuli. Responses to darks are stronger, faster, and driven by a larger number of cortical neurons than responses to lights. Here, we demonstrate that these light-dark cortical asymmetries reflect a functional specialization of ON and OFF pathways for different stimulus properties. We show that large long-lasting stimuli drive stronger cortical responses when they are light, whereas small fast stimuli drive stronger cortical responses when they are dark. Moreover, we show that these light-dark asymmetries are preserved under a wide variety of luminance conditions that range from photopic to low mesopic light. Our results suggest that ON and OFF pathways extract different spatiotemporal information from visual scenes, making OFF local-fast signals better suited to maximize visual acuity and ON global-slow signals better suited to guide the eye movements needed for retinal image stabilization.

Graphical Abstract

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AUTHOR CONTRIBUTIONS
R.M. and J.-M.A. designed the experiments and wrote the paper. R.M., J.J., C.P., and J.-M.A. participated in the experiments and data analysis.

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DECLARATION OF INTERESTS
The authors declare no competing interests.
In Brief

Mazade et al. find pronounced differences in the stimulus preferences of cortical pathways signaling lights (ON) and darks (OFF) in visual scenes. ON-preferred stimuli are large and steady, while OFF are small and brief. These results suggest an ON/OFF pathway specialization in global-slow and local-fast vision.

INTRODUCTION

The brain processes light and dark features in an image using two visual pathways that signal local luminance increments (ON) and decrements (OFF). ON and OFF pathways show pronounced asymmetries that begin at the retina (Chichilnisky and Kalmar, 2002; Dacey and Petersen, 1992; Pandarinath et al., 2010; Peichl et al., 1987; Ravi et al., 2018) and are further amplified in the cortex (Jin et al., 2008; Yeh et al., 2009; Zemon et al., 1988). In cat primary visual cortex, the OFF pathway is stronger and faster, covers more cortical territory, and responds more linearly to changes in luminance than the ON pathway (Jin et al., 2008, 2011; Komban et al., 2014; Kremkow et al., 2014; Rekauzke et al., 2016; Taylor et al., 2018; Wang et al., 2015). Moreover, darks generate stronger cortical responses than lights in humans, macaques, cats, and mice (Jimenez et al., 2018; Jin et al., 2008, 2011; Kremkow et al., 2014; Xing et al., 2010; Yeh et al., 2009; Zemon et al., 1988; Zurawel et al., 2014), and the OFF pathway also acts as a retinotopy anchor of visual cortical topography in different animals (Jimenez et al., 2018; Kremkow et al., 2016; Lee et al., 2016).
ON and OFF pathways, along with rod (scotopic) and cone (photopic) pathways, can process a wide luminance range that spans 10,000 cd/m$^2$ (Frazor and Geisler, 2006; Pons et al., 2017; Shapley and Enroth-Cugell, 1984). OFF cortical responses are known to be stronger than ON cortical responses in scenes dominated by mid-luminance backgrounds, low spatial frequencies, and optical blur (Kremkow et al., 2014; Pons et al., 2017). However, it remains unclear what stimulus conditions (if any) make ON cortical responses stronger than OFF cortical responses. In cats, scotopic light levels can switch some cortical responses from OFF to ON dominated (Ramoa et al., 1985). However, in humans, darks remain more salient than lights under low mesopic light (Pons et al., 2017).

Several lines of evidence indicate that ON cortical responses may play an important role in signaling slow motion in visual scenes. Flies rely on the ON pathway to detect slow image motion (Leonhardt et al., 2016), and humans are more accurate at detecting light than dark slow-moving bars (Luo-Li et al., 2018). In rodents and lagomorphs, direction-selective ON retinal ganglion cells show a preference for slow velocities (Oyster, 1968; Sun et al., 2015), and, without the ON pathway, zebrafish lose the optokinetic reflex triggered by slow directional motion (Emran et al., 2007). Conversely, several lines of evidence indicate that OFF visual responses are important for processing fast changes of small targets. The OFF pathway generates faster responses (Jin et al., 2011; Komban et al., 2014; Nichols et al., 2013; Rekauzke et al., 2016) and has greater spatial resolution than the ON pathway (Jimenez et al., 2018; Kremkow et al., 2014, 2016; Lee et al., 2016). Moreover, humans and monkeys with defective ON pathways can have normal visual acuity, as measured with standard tests using dark stimuli on bright backgrounds (Dolan and Schiller, 1994; Dryja et al., 2005).

Based on this evidence, we hypothesized that ON and OFF cortical pathways are specialized in processing different spatio-temporal properties of visual scenes. Here, we provide strong support for this hypothesis by demonstrating pronounced differences in the stimulus spatiotemporal preferences of ON and OFF pathways, in their size suppression, temporal suppression, and temporal contrast. Some of these ON-OFF spatiotemporal differences can be as pronounced as the differences between Y and X pathways in cats or between magnocellular and parvocellular pathways in primates. The pronounced ON-OFF spatiotemporal differences that we discovered make large long-lasting stimuli to generate stronger ON than OFF cortical responses and small fast stimuli to generate stronger OFF than ON cortical responses. We show that this functional specialization of ON and OFF cortical pathways is robust, is maintained under a wide variety of luminance conditions (from photopic to low mesopic light levels), and has a correlate in the statistics of natural scenes.

RESULTS

We investigated differences in spatiotemporal processing between ON and OFF cortical pathways by measuring visual cortical responses to dark (0.27 cd/m$^2$) and light (239 cd/m$^2$) stimuli. The stimuli were square targets presented on light (239 cd/m$^2$), dark (0.27 cd/m$^2$), or midgray (120 cd/m$^2$) backgrounds that could have different sizes (from 1 to 23 deg), durations (from 16 to 133 ms), and luminance (from a maximum of 0.024 to 239 cd/m$^2$).
Throughout the paper, we use the term “maximum-contrast background” when referring to ON and OFF responses measured in dark or light backgrounds respectively, and “midgray background” when referring to ON and OFF responses measured in the same midgray background. ON responses are generated by turning on light targets (ON onset responses) or turning off dark targets (ON rebound responses), whereas OFF responses are generated by turning on dark targets (OFF onset responses) or turning off light targets (OFF rebound responses).

The results below provide a detailed description of differences in spatiotemporal tuning, size suppression, temporal suppression, and temporal contrast between ON and OFF cortical responses that, together with measurements of natural scenes, support a functional specialization of ON and OFF pathways in global-slow and local-fast vision. These pronounced spatiotemporal differences may explain why ON and OFF pathways remain segregated in cat visual cortex (Kremkow et al., 2016), as is also the case for Y and X pathways in cats or magnocellular and parvocellular pathways in primates.

Cortical Response Preference for Small-Fast Dark Stimuli and Large-Slow Light Stimuli

Our results demonstrate that the relative strength of ON and OFF cortical responses is strongly dependent on the spatiotemporal properties of the stimuli (Figure 1). On maximum-contrast backgrounds, cortical responses were stronger to darks than lights when the stimuli were small and fast (presented at fast rates) and stronger to lights than darks when the stimuli were large and slow (presented at slow rates). These differences in spatio-temporal preference were most pronounced at the response onset but could also be demonstrated at the response rebound. For example, in the cortical multiunit site illustrated in Figure 1A, turning on a 4-deg/16-ms target drove 311% stronger OFF than ON onset responses (Figure 1A, black arrow in 16-ms column, 233.3 spk/s to darks versus 56.7 spk/s to lights). Moreover, turning off a 4-deg/83-ms target also drove 148% stronger OFF than ON rebound responses (Figure 1A, black arrow in the right of 83-ms column, 147.4 spk/s to lights versus 59.4 spk/s to darks).

Whereas small fast targets drove stronger OFF than ON cortical responses, larger slower targets drove stronger ON than OFF cortical responses. For example, in the cortical site illustrated in Figure 1A, turning on a 23-deg/133-ms target drove 349% stronger ON than OFF cortical onset responses (Figure 1A, gray arrow on the left of 133-ms column, 159.4 spk/s to lights versus 35.5 spk/s to darks). Moreover, turning off a 23-deg/133-ms target also drove 190% stronger ON than OFF rebound responses (Figure 1A, gray arrow in the right of 133-ms column, 178.4 spk/s to darks versus 61.6 spk/s to lights). The spatiotemporal differences between cortical responses to lights and darks could be demonstrated in individual cortical recording sites (Figure 1A) and in the average across all recording sites (Figures 1B and 1C).

The differences between ON and OFF cortical responses were most pronounced when light and dark targets were presented on maximum-contrast backgrounds. On midgray backgrounds, cortical responses became weaker because the stimuli used only half the luminance range of the monitor (Figures S1A–S1C, ~120 cd/m² for midgray versus ~239 cd/m² for maximum-contrast backgrounds). On this reduced luminance and response range,
OFF cortical responses became stronger than ON cortical responses under most stimulus conditions (average response onset across 4- to 23-deg sizes and 16- to 83-ms durations: 61.1 ± 0.6 versus 36.7 ± 0.4 spk/s, p < 0.001, Wilcoxon test). However, the ON/OFF response balance still changed with the spatiotemporal properties of the stimulus (Figures S1A–S1C). Importantly, whereas the relative strength of ON and OFF cortical responses was strongly modulated by the stimulus properties, the light-dark temporal differences generated by the liquid-crystal display (LCD) monitor were small, constant, and independent of stimulus size, duration, and background luminance (Figures S1D–S1G). These results demonstrate that, in maximum-contrast backgrounds, cortical neurons show a preference for dark stimuli that are small and fast and light stimuli that are large and slow, consistent with a functional specialization of OFF and ON pathways for small-fast and large-slow stimuli.

**Spatiotemporal Tuning of OFF and ON Cortical Responses**

At the fastest presentation rate (16-ms duration), OFF cortical responses were stronger than ON cortical responses for nearly all target sizes that we tested except the smallest one (Figure 2A). Only when the target duration increased did OFF cortical responses become equal or weaker than ON cortical responses (Figures 2A–2H). On maximum-contrast backgrounds, brief 33-ms stimuli generated stronger ON than OFF cortical responses when the stimulus became more than two times larger than the average cortical receptive field from an individual cortical site (Figure 2B, >14 deg; average receptive field size: 7.1 ± 0.1 deg). On average, a stimulus presented for 33 ms on maximum-contrast backgrounds elicited 18% stronger OFF than ON cortical responses when its size was 7 deg (Figure 2B, 104.3 ± 2.8 versus 88.7 ± 2.2 spk/s; p < 0.001, Wilcoxon test), equally strong ON and OFF responses when the size increased by two times (Figure 2B, 14 deg; 79.8 ± 2.2 versus 80.2 ± 2.1 spk/s; p = 0.700, Wilcoxon test), and 20% stronger ON than OFF responses when the size increase by nearly three times (Figure 2B, 20 deg; 64.6 ± 1.9 versus 77.7 ± 2.2 spk/s; p < 0.001, Wilcoxon test). At the slowest presentation rates (83 and 133 ms), maximum-contrast backgrounds made ON cortical responses stronger than OFF cortical responses for almost all target sizes (Figures 2C and 2D).

The reduction in OFF response dominance with stimulus duration could also be demonstrated on midgray backgrounds. On midgray backgrounds, most dark stimuli drove stronger cortical responses than light stimuli (Figures 2E–2G), and this dark cortical dominance could only be reduced with long stimulus durations (Figure 2H). OFF and ON cortical responses were most similar when the stimulus lasted 133 ms (e.g., Figure 2H, 11 deg/133 ms, 50.8 ± 2.3 versus 49.8 ± 2.1 spk/s; p = 0.409, Wilcoxon test) and most different when the stimulus duration matched the duration of the cortical response transient, which was around 30 ms (Figure 2F, 7 deg/33 ms, 88.2 ± 3.4 versus 52.1 ± 2.1 spk/s; p < 0.001, Wilcoxon test; see STAR Methods for measurements of response transients). These results demonstrate that brief stimuli generate stronger OFF than ON cortical responses, but this OFF dominance decreases with stimulus duration, consistent with a functional specialization of ON and OFF pathways in processing different stimulus speeds.
Stronger OFF Than ON Size Suppression on Maximum-Contrast Backgrounds

Large slow stimuli suppressed 3.6 times more OFF than ON cortical responses on maximum-contrast backgrounds (Figures 2I–2K, 46.6% for OFF versus 13.0% suppression for ON; p < 0.001, Wilcoxon test, 133-ms stimuli). However, on midgray backgrounds, the average ON size suppression increased by 180%, while the OFF size suppression was only increased by 1.4% (Figures 2I and 2L, average across all stimulus durations for maximum-contrast versus midgray backgrounds: 19.9% versus 55.8% for ON responses, p < 0.001; 42.5% versus 43.1% for OFF responses; p = 0.041, Wilcoxon test). Consequently, whereas the average size suppression was 2.1 times stronger for OFF than ON responses on maximum-contrast backgrounds, midgray backgrounds made the size suppression slightly stronger (1.3 times) for ON than OFF responses (Figures 2L–2N). These results demonstrate that ON cortical size suppression is strongly dependent on background luminance. It is weak on maximum-contrast backgrounds but becomes slightly stronger than OFF size suppression on midgray backgrounds.

Stronger OFF Than ON Temporal Response Suppression

Cortical responses were suppressed by the temporal duration of the stimuli. This temporal suppression was much stronger for darks than lights across all stimulus conditions (Figures 3A and 3B). On maximum-contrast backgrounds, OFF cortical responses were strongest when the stimuli were brief (16–33 ms) and became 41% weaker when the stimulus duration increased to 133 ms regardless of stimulus size (Figure 3A, blue lines; average maximum response across 4- to 23-deg targets: 94.2 ± 1.0 spk/s for 16 ms stimuli versus 55.8 ± 0.7 spk/s for 133-ms stimuli; p < 0.001, Wilcoxon test). Conversely, ON cortical responses were facilitated by stimulus duration (not suppressed) and were 11% weaker to fast than slow stimuli (Figure 3A, red lines; average maximum response across 4- to 23-deg targets: 81.3 ± 0.8 spk/s for 16-ms stimuli versus 90.9 ± 0.9 spk/s for 133-ms stimuli; p < 0.001, Wilcoxon test). Small stimuli required the longest stimulus durations to equalize the strength of OFF and ON responses (Figure 3A, 4 deg panel). However, as the stimulus size increased, the stimulus duration needed to switch from OFF to ON dominance decreased (Figure 3A, 83 ms for 7- to 11-deg targets and 33 ms for 14- to 23-deg targets).

Similarly, on midgray backgrounds, the cortical OFF dominance was reduced most strongly when the stimuli were slow (Figure 3B). The ON and OFF temporal response suppression was similar for the smallest stimuli but became very different when the stimulus size increased (Figures 3C and 3F). This result could be replicated in both maximum-contrast backgrounds (Figures 3C–3E, 17 deg, 47.8% ± 1.5% OFF suppression versus 8.0% ± 1.1% ON facilitation; p < 0.001, Wilcoxon test) and midgray backgrounds (Figures 3F–3H, 17 deg, 41.6% ± 1.7% OFF suppression versus 42.4% ± 3.4% ON facilitation; p < 0.001, Wilcoxon test). The finding that temporal suppression is stronger for dark than light stimuli is consistent with a functional specialization of ON and OFF pathways in processing different temporal properties of the stimuli.

Higher OFF Than ON Temporal Contrast Sensitivity

Just as spatial contrast can be defined as a difference in dark-light luminance over space, temporal contrast can be defined as a difference in dark-light luminance over time.
Therefore, increasing the duration of the adapting stimulus that generates a rebound response is equivalent to increasing temporal contrast. Increasing temporal contrast made both OFF and ON rebound responses stronger (Figure 4A; notice that blue illustrates ON responses to dark targets turned off, and red illustrates OFF responses to light targets turned off). Interestingly, temporal and spatial contrast had opposite effects on ON/OFF response balance. Whereas low spatial contrast generates stronger ON than OFF cortical responses (Kremkow et al., 2014), low temporal contrast generated stronger OFF than ON cortical responses (Figures 4A and 4B, left panels, 16- to 33-ms stimuli). Similarly, whereas high spatial contrast generates stronger OFF than ON cortical responses (Kremkow et al., 2014), high temporal contrast generated stronger ON than OFF rebound responses (Figures 4A and 4B, left panels, 133-ms stimuli). This effect could be replicated on different backgrounds (Figures 4A and 4B) and was very robust, as verified by plotting the size tuning of rebound responses (Figures 4C and 4D).

On average, low temporal contrast (33-ms adapting stimuli) drove 56% stronger OFF than ON cortical responses on maximum-contrast backgrounds (Figure 4A, left panel, 33-ms bin, 51.8 ± 0.7 for light off versus 33.3 ± 0.5 spk/s for dark off; p < 0.001, Wilcoxon test) and 40% stronger OFF than ON cortical responses on midgray backgrounds (Figure 4B, left panel, 33-ms bin, 40.8 ± 0.7 for light off versus 29.2 ± 0.5 for dark off; p < 0.001, Wilcoxon test). Conversely, high temporal contrast (133-ms adapting stimuli) drove 8% stronger OFF than OFF cortical responses on maximum-contrast backgrounds (Figure 4A, left panel, 133-ms bin, 90.3 ± 0.8 for dark off versus 83.4 ± 0.8 spk/s for light off; p < 0.001, Wilcoxon test) and 16% stronger OFF than ON cortical responses on midgray backgrounds (Figure 4B, left panel, 133-ms bin, 62.4 ± 0.9 for dark off versus 53.8 ± 0.9 spk/s for light off; p < 0.001, Wilcoxon test).

These results demonstrate that, regardless of background conditions (maximum-contrast or midgray) and temporal history (onset or rebound responses), brief stimuli always generate stronger OFF than ON cortical responses. Moreover, whereas low temporal contrasts drive stronger OFF responses, high temporal contrasts drive stronger ON responses, a finding that is again consistent with a functional specialization of ON and OFF pathways in signaling different temporal properties of the stimulus.

**Cortical Responses Signal the Time Course of Dark Stimuli Better Than Light Stimuli**

Brief stimuli always generated stronger onset than rebound responses and the onset/rebound ratios were consistently higher for darks than lights (Figures 4E and 4F, average onset/rebound ratio for 16-ms stimuli on maximum-contrast background: 2.7 versus 1.8; p < 0.001; on midgray backgrounds: 3.8 versus 1.4; p < 0.001, Wilcoxon tests). However, as the stimulus duration increased, rebound responses became stronger or equal to onset responses and the onset/rebound ratios became lower for darks than lights (Figures 4E and 4F, average onset/rebound ratio for 133-ms stimuli on maximum-contrast background: 0.8 for darks versus 1.2 for lights; on midgray backgrounds: 0.9 for darks versus 1.1 for lights; p < 0.001, Wilcoxon tests). Dark stimuli generated stronger onset than rebound responses across nearly all conditions except when using the largest slowest stimuli (Figures 4E and 4F, blue plots). In contrast, light stimuli generated stronger onset than rebound responses across nearly all
conditions except for 33- to 83-ms stimuli on midgray backgrounds (Figures 4E and 4F, red plots).

Strong onset responses signal the time of stimulus appearance whereas strong rebound responses signal the time of stimulus disappearance. Therefore, our results indicate that cortical responses signal better the appearance of brief dark than light stimuli (higher onset/rebound ratios for brief darks). They also indicate that cortical responses signal better the disappearance of slow dark than light stimuli (stronger rebounds that make onset/rebound ratios lower for slow darks). These results are again consistent with a functional specialization of OFF pathways in processing more accurately stimulus timing than ON pathways.

**Low Light Affects Similarly the Strength of ON and OFF Cortical Responses**

The results above demonstrate that the balance of ON and OFF cortical responses is modulated by the size, timing, and background luminance of the stimulus. An additional important parameter that could change the ON/OFF response balance is the amount of light entering the eye. As the amount of light decreases to mesopic levels (0.1–10 cd/m² in the cat; see Figures S2A–S2C and STAR Methods), the activation of ON-dominated rod pathways could potentially shift the ON/OFF cortical response balance toward ON dominance. Therefore, to investigate how ON and OFF cortical pathways are affected by low light, we measured cortical responses to dark and light sparse noise stimuli (2.8 deg, 33 ms) on different backgrounds, while reducing light level by placing neutral density filters in front of the eye.

Our results demonstrate that reducing the amount of light to mesopic levels makes visual cortical responses weaker and slower but does not cause a major change in ON/OFF cortical response balance. In OFF cortical domains (Figure 5A), responses to the onset of darks were consistently stronger than responses to the onset of lights at all luminances except at the scotopic level (0.04 cd/m²). Similarly, in ON cortical domains (Figure 5B), responses to the onset of lights were stronger than responses to the onset of darks across all light levels. Reducing the amount of light increased the latency of cortical responses, as can be seen in the example cortical sites from Figures 5A and 5B. However, the changes were roughly similar for darks and lights (Figures 5C and 5D). The cortical response latency increased by ~12 ms per log-unit of luminance when using the entire luminance range of the monitor (Figure 5C, 239 cd/m², 12.1 slope and R² of 0.99 for darks, 12.5 slope and R² of 0.98 for lights) and by ~11 ms when using midgray backgrounds with stimuli spanning only half the luminance range (Figure 5D, 120 cd/m², 11.3 slope and R² of 0.97] for darks, 10.7 slope and R² of 0.95 for lights).

Small sparse noise stimuli were still able to drive strong ON and OFF cortical responses when the amount of light was reduced by three logarithmic units from 70 to 0.07 cd/m² (Figures 5A and 5B). Moreover, cortical responses remained stronger to dark than light stimuli through low mesopic luminance levels, on both maximum-contrast backgrounds (Figure 5E, left panel; 0.7 cd/m², 47.2 ± 1.2 versus 35.1 ± 0.8 spk/s; p < 0.001, Wilcoxon test) and midgray backgrounds (Figure 5F, left panel; 0.7 cd/m², 46.1 ± 1.5 versus 26.9 ± 0.8 spk/s; p < 0.001, Wilcoxon test). Only under scotopic light did the responses to dark stimuli...
become weaker (Figure 5E, left panel; 0.007 cd/m$^2$, 18.2 ± 0.9 versus 26.1 ± 1.2 spk/s; p < 0.001, Wilcoxon test) or equal to the responses to light stimuli (Figure 5F, left panel; 0.007 cd/m$^2$, 17.0 ± 1.1 versus 14.6 ± 0.8 spk/s; p = 0.704, Wilcoxon test).

OFF cortical rebound responses (to light off) tended to be stronger than ON cortical rebound responses (to dark off) under most light levels, even under scotopic light (Figure 5E, middle panel). Only on midgray backgrounds did OFF rebound responses became equal (at scotopic light) or weaker (at photopic light) than ON rebound responses (Figure 5F, middle panel). Finally, when onset and rebound responses were summed, OFF cortical responses dominated over ON cortical responses at all light levels and background conditions except under scotopic light (Figures 5E and 5F, right panels). Therefore, we conclude that the balance between ON and OFF cortical responses remains stable and consistently biased toward OFF cortical dominance across very different light levels.

As with ON/OFF response balance, the average cortical receptive field size was not greatly affected by low light (Figure S3). As the stimulus luminance was reduced, the receptive field size remained roughly stable in both OFF (Figure S3A) and ON cortical domains (Figure S3B), but the signal-to-noise ratio of the response decreased (Figures S3C and S3D, slopes: 2.2, $R^2$ of 0.98, p = 0.001 for darks and 1.2, $R^2$ of 0.88, p = 0.018 for lights on maximum-contrast background; 2.0, $R^2$ of 0.99 for darks and 1.4, $R^2$ of 0.99 for lights on midgray backgrounds; p < 0.001). Because of the reduction in signal-to-noise, the receptive fields could appear larger at low light but mostly because the visual responses became noisier. Consistent with this interpretation, the average ON and OFF cortical receptive fields were ~50% larger at scotopic (0.007 cd/m$^2$) than photopic light (70 cd/m$^2$) when we selected receptive fields with a signal-to-noise ratio larger than 5 (Figures S3E and S3F, left panels). However, when we selected receptive fields with a signal-to-noise ratio larger than 10, the receptive field size at scotopic light was just as large (or slightly smaller) than under photopic light (Figures S3E and S3F, right panels). Because the signal-to-noise is higher for OFF than ON receptive fields (Figures S3C and S3D), increasing the signal-to-noise criteria also made the OFF average receptive field slightly larger than the ON average receptive field.

Taken together, these results demonstrate that low light makes cortical responses noisier and slower but keeps the ON/OFF response balance and receptive field size relatively unchanged. Therefore, we conclude that ON/OFF cortical response balance is relatively independent of retinal illumination within the photopic-mesopic range.

**Low Light Affects More ON Than OFF Size Suppression**

Although low light affected similarly the strength and latency of ON and OFF cortical responses, it had a different effect on ON and OFF spatiotemporal suppression. A change from photopic to mesopic light reduced ON size suppression 4–10 times more than OFF size suppression (Figures 6A and 6B, 237.0% reduction for ON versus 23.6% for OFF on maximum-contrast backgrounds; 78.8% reduction for ON versus 20.7% for OFF on midgray backgrounds; p < 0.001, chi-square tests; see also Figures S4A and S4B). As a consequence, at mesopic light, the differences in spatial suppression between ON and OFF responses became independent of background luminance (maximum contrast or midgray).

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Reducing the amount light from photopic to mesopic levels also weakened the OFF temporal response suppression by 59% on maximum-contrast backgrounds (Figure 6C, 46.7% ± 0.5% versus 19.3% ± 1.5% suppression) and 55% on midgray backgrounds (Figure 6D, 48.2% ± 0.6% versus 21.8% ± 0.8% suppression). However, once again, the OFF temporal response suppression was preserved at mesopic light (Figures 6C and 6D; see also Figures S4C and S4D), while the ON temporal facilitation became increasingly stronger as the amount of light decreased (Figure 6C, photopic/mesopic/scotopic: −14.2% ± 0.8%−45.1% ± 1.7%/−148.7% ± 20.0% facilitation on dark backgrounds; Figure 6D, −8.3% ± 1.4%/−17.7% ±1.4%−85.3% ± 8.0% facilitation on midgray backgrounds). Low light also reduced the rebound responses (Figures S5A–S5D); however, OFF rebound responses remained consistently stronger than ON rebound responses across most stimulus conditions, even under scotopic light.

We conclude that low light makes visual cortical responses weaker, slower, noisier, and less spatiotemporally defined (less suppressed by size and temporal duration) while preserving the cortical OFF dominance and OFF spatiotemporal suppression needed to process local-fast vision even under low light.

**Image Stabilization Is More Accurate When Using Light Than Dark Regions of Visual Scenes**

The results presented above suggest a functional specialization of OFF pathways for processing small fast stimuli and ON pathways for processing large slow stimuli. The higher spatiotemporal resolution of the OFF pathway seems ideal to maximize visual acuity and is consistent with the higher spatiotemporal resolution for darks than lights demonstrated in human vision (Komban et al., 2014; Pons et al., 2017) and cortical retinotopy (Kremkow et al., 2014, 2016; Lee et al., 2016). Conversely, the ON response preference for large slow stimuli (and weak temporal suppression) seems ideal for signaling slow drifts of large image regions during self-motion and guiding the eye movements needed for retinal image stabilization.

We hypothesize that the ON pathway responds better to large slow stimuli than the OFF pathway because most visual scenes have larger light than dark regions, and these large light regions allow a more accurate stabilization of the retinal image during self-motion. To test this hypothesis, we took all images from the McGill Calibrated Color Image Database (Olmos and Kingdom, 2004), converted them to a grayscale, and split each image into two: an image of darks and an image of lights. The images of darks and lights were first passed through different ON and OFF luminance response functions that applied larger neuronal blur to lights than darks, consistent with our previous experimental results (Kremkow et al., 2014; Pons et al., 2017). Then, the images were convolved with two separate difference-of-Gaussian functions that applied stronger surround suppression to darks than lights (Figure 7A), consistent with the new experimental measurements described above. Eye movements should generate the strongest ON and OFF cortical responses when the temporal contrast is highest (i.e., a cortical receptive field falls in the lightest and darkest regions of the image). Therefore, we selected the pixel regions of the image with the darkest and lightest values (top 10 percentile for each polarity) and then ran an image stabilization test. In this test, we
moved the retinal image by 200 pixels to simulate a brief horizontal self-motion. Then, we applied a MATLAB algorithm of image alignment (“im-register”) to correct the image displacement (e.g., simulate the eye movement that brings the image to the original position before the movement).

Because ON responses have a preference for large slow stimuli, we predicted that the image of lights should have fewer, larger, and more homogeneous image regions than the image of darks. In turn, the large homogeneous light regions should allow a more accurate image realignment than the more numerous fine-grained dark regions (Figure 7A). In support of our prediction, the largest region size within each image was frequently light (Figure 7B, 1,161 versus 153 images; p < 0.0001, chi-square test), whereas dark regions outnumbered light regions in most images (1,145 versus 141 images; p < 0.0001, chi-square test). The average region size was also larger for lights than darks (Figures 7B and 7D, 10^{5.6} ± 10^{0.01} versus 10^{5.0} ± 10^{0.03} pixels; p < 0.001, Wilcoxon test), whereas the average number of regions was larger for darks than lights (642.8 ± 17.7 versus 263.7 ± 6.9; p < 0.001, Wilcoxon test).

These pronounced differences in region size and number made image alignment more accurate for lights than darks (Figure 7C; mean ± SD: 0.96 ± 0.03 versus 0.83 ± 0.13; p < 0.001, Wilcoxon test, with 1 being perfect alignment). Moreover, the more precise alignment for lights could be replicated across different image categories (Figure 7E) and was present even if we minimized the ON-OFF differences in neuronal blur and surround suppression (Figure S6). Interestingly, without ON-OFF filter differences, image alignment was still better for lights than darks (Figure S6F, 0.63 ± 0.01 versus 0.58 ± 0.01 alignment; p < 0.001, Wilcoxon test) even if the largest regions were dark (Figure S6H; average size, 10^{4.3} ± 10^{0.03} pixels for darks versus 10^{4.0} ± 10^{0.03} pixels for lights; p < 0.001, Wilcoxon test). The reason is that dark regions continue to outnumber light regions (2,974.2 ± 85.5 versus 1,122.7 ± 65.6; p < 0.001, Wilcoxon test) and the larger number of fine-grained regions made the image alignment less accurate for darks. This result provides further support to our conclusion that signals from the ON pathway are better suited for image retinal stabilization than signals from the OFF pathway.

**DISCUSSION**

Our results demonstrate that the primary visual cortex prefers dark stimuli that are small and fast, and light stimuli that are large and slow. We show that these preferences result from pronounced differences in the spatiotemporal properties of OFF and ON visual cortical responses. OFF cortical responses are driven by faster and smaller stimuli, are suppressed by larger and slower stimuli, and have higher temporal contrast sensitivity than ON cortical responses. Moreover, we show that reducing the amount of light makes cortical responses weaker, slower, noisier, and less spatiotemporal defined (i.e., less spatiotempo-rally suppressed) but does not cause pronounced changes in the ON and OFF spatiotemporal preferences and average ON/OFF response balance (OFF responses continue to be stronger than ON responses on average). The pronounced dark-light asymmetries that we demonstrate strongly suggest that ON and OFF visual cortical pathways are specialized in
processing different spatiotemporal properties of the visual scene. The OFF pathway is better tuned to maximize visual acuity and the ON pathway to minimize motion blur.

**ON and OFF Functional Specialization in Different Species**

ON and OFF visual pathways are well preserved throughout the animal kingdom from flies to primates (Dacey and Petersen, 1992; Joesch et al., 2010), and their basic retinal wiring is remarkably similar in different vertebrates. In all vertebrates, OFF bipolar cells have faster receptors and shorter length than ON bipolar cells (Euler et al., 2014), and in many vertebrates, OFF retinal ganglion cells have smaller dendritic arbors than ON retinal ganglion cells (Dacey and Petersen, 1992; Wässle et al., 1981). The OFF pathway tends to respond faster to visual stimuli than the ON pathway (Jin et al., 2011; Komban et al., 2014; Rekauzke et al., 2016), and humans are faster at detecting dark than light flashed stimuli (Komban et al., 2014; Pons et al., 2017).

In contrast to the OFF pathway, the ON pathway processes slow motion better than the OFF pathway in invertebrates and fish (Emran et al., 2007; Leonhardt et al., 2016). Moreover, in rodents and lagomorphs, the ON pathway is specialized in processing motion direction along the three axes of the semicircular canals that are used for self-motion image stabilization, a pathway that may be preserved across mammals (Berson, 2008). Humans also see slow motion better with light than dark stimuli (Luo-Li et al., 2018), and human visual acuity can be preserved in the absence of ON pathway (Dryja et al., 2005). Moreover, genetic defects of the ON pathway can cause nystagmus in humans (Dryja et al., 2005), which is a deficit in retinal image stabilization. Taken together with these previous studies, our results suggest that OFF and ON pathways are specialized in extracting different spatiotemporal properties of visual scenes, and that this functional specialization is preserved across species spanning from invertebrates to humans.

The finding that large slow stimuli drive stronger ON than OFF cortical responses has clear implications for natural vision. For example, eye blinks are assumed to drive equally strong ON and OFF cortical responses; however, our results suggest that they should drive stronger ON responses. Closing the eyes expose the retinas to large dark long (>100 ms) stimuli that should suppress OFF responses, whereas opening the eyes expose the retinas to large light long stimuli that should drive strong ON responses. In humans, eye blinks expose the retina to large dark-light stimulus flickers every 3–15 s (Bentivoglio et al., 1997). Therefore, if the ON and OFF thalamocortical pathways are evolutionarily preserved, the low-frequency eye blinks of humans (generating large slow dark-light stimuli) should drive stronger ON than OFF cortical responses.

The ON response preference for large slow stimuli also seems ideal to track image self-motion during natural vision. In visual scenes, large light patches that are static (e.g., sky patches) can serve as excellent positional references to track self-motion, which changes image position at frequencies of less than 10 Hz (Carriot et al., 2017). In addition, the ON neuronal blur can make large patches more salient by enlarging them and removing dark small areas within the patch (Komban et al., 2014; Kremkow et al., 2014; Pons et al., 2017). Our analysis of visual scenes supports this hypothesis by demonstrating that image motion stabilization is more accurate when using light than dark patches of visual scenes.
Changing ON/OFF Response Balance toward ON Dominance

The stimulus dependency of ON/OFF response balance complicates the interpretation of traditional measurements of stimulus tuning in primary visual cortex. Previous measurements assumed that the light and dark cycles of a grating contributed similarly to the cortical response. Moreover, they assumed that contribution of light and dark cycles remained equal across changes in grating size, temporal frequency, luminance, and contrast. Our results demonstrate that both of these assumptions are incorrect. Whereas the cortical tuning for stimulus orientation is relatively independent of contrast polarity (Kremkow et al., 2014), the tuning for many other stimulus properties is not.

Gratings with low spatial frequencies drive stronger OFF than ON cortical responses (Jansen et al., 2019; Kremkow et al., 2014; Onat et al., 2011) probably because the neuronal blur expands more the light than dark cycles of the grating and the light cycles activate more surround suppression (Kremkow et al., 2016; Pons et al., 2017). Unlike grating patterns, however, uniform large surfaces (>2 times the receptive field size) drive stronger ON than OFF cortical responses, particularly when the target duration is long and the temporal contrast is high. The larger and longer the stimulus target, the more pronounced the ON cortical dominance. Therefore, taken together with previous studies, our results suggest that exposing the retina to low spatial frequency patterns (e.g., optical blur and/or low light) makes visual cortical responses more OFF dominated (Pons et al., 2017), whereas exposing the retina to large homogeneous bright surfaces (e.g., sky patches) makes visual cortical responses more ON dominated.

ON-OFF Differences in Spatiotemporal Suppression

The stronger suppression within the OFF cortical pathway seems ideal to maximize the spatiotemporal salience of small brief stimuli. Temporal suppression makes OFF cortical responses strongest when the stimulus is brief, enhancing the detection of brief targets. Similarly, size suppression makes OFF cortical responses strongest when the stimulus is small, enhancing the discrimination of small targets in crowded backgrounds. Unlike OFF visual responses, ON visual responses are not suppressed but facilitated by increasing stimulus duration. Therefore, ON visual responses are better signals to track image position changes during self-motion, which tend to be slow (Carriot et al., 2017).

Unlike OFF spatial suppression, ON spatial suppression depends strongly on background luminance; it is nearly absent on dark backgrounds and becomes stronger than OFF spatial suppression on midgray backgrounds. The pronounced spatial suppression of light stimuli was previously demonstrated in primate visual cortex for both baseline cortical activity (Xing et al., 2014) and in response to stimuli presented on midgray backgrounds (Zurawel et al., 2014). Because midgray backgrounds make ON luminance response functions more linear, they reduce the neuronal blur of light stimuli (Kremkow et al., 2014; Pons et al., 2017). Therefore, taken together with previous work, our results suggest that midgray backgrounds increase size suppression and decrease neuronal blur, allowing for a better discrimination of light targets on light backgrounds (e.g., bright clouds on bright sky). Also, because midgray backgrounds reduce temporal contrast, they reduce the strength of ON responses through at least two different mechanisms: an increase in size suppression and a
decrease in temporal contrast. These results lead to a counterintuitive prediction. While looking at a bright sky, eye blinks should drive ON responses that are just as strong as ON responses driven by bright targets on dark backgrounds (i.e., maximum temporal contrast, neuronal blur, and spatial summation). Only after the effect of the high temporal contrast declines, the sustained suppression of baseline activity should make ON visual responses similar to those generated on midgray backgrounds (i.e., maximum size suppression and minimum neuronal blur).

The Effect of Background Luminance on ON and OFF Spatiotemporal Properties

Our results demonstrate that ON-OFF temporal differences are independent of background luminance, but ON-OFF spatial differences are not. Maximum-contrast backgrounds made OFF size suppression much stronger than ON size suppression, whereas photopic midgray backgrounds made ON size suppression slightly stronger than OFF size suppression. Importantly, when the amount of light was reduced to mesopic levels, OFF size suppression was consistently stronger than ON size suppression regardless of background conditions. Therefore, OFF size suppression is stronger than ON size suppression under most stimulus conditions except on midgray photopic backgrounds. It is also important to emphasize that ON and OFF responses were only matched in strength in maximum-contrast backgrounds: light background for OFF and dark background for ON. Consistent with this result, human and monkey deficits in the ON visual pathway are best detected when the ON pathway is maximally activated with light stimuli on dark backgrounds (Dolan and Schiller, 1994; Dryja et al., 2005).

Possible Implications of the ON and OFF Functional Specialization for Visual Disease

The ON-OFF spatiotemporal differences that we demonstrate in visual cortex can be as pronounced as the spatiotemporal differences between X and Y pathways in cats and parvocellular and magnocellular pathways in primates. If as for the X-Y and parvocellular-magnocellular differences, the spatiotemporal ON-OFF differences are inherited from the retina, our results could have important implications for visual disorders associated with deficits in ON retinal function. For example, myopia (a disease that prevents focusing images at far distances) has been associated with a deficit in retinal dopamine, which is released only by dopaminergic ON amacrine cells in the retina (Zhou et al., 2017). For reasons that remain unknown, exposure to low light, reading, and optical blur increases the risk of developing myopia, whereas spending time outdoors reduces it (Rose et al., 2008). If myopia is caused by an understimulation of ON visual pathways, our results could bring new ideas on how prevent myopia progression. In particular, bright large slow targets (e.g., sky patches) seen while blinking should boost ON visual responses, a prediction that supports old beliefs that blinking protects against myopia (Bates, 1920). In turn, low light and optical blur should weaken ON responses (Pons et al., 2017) and explain why reading at low light increases myopia. Future research is needed to investigate possible new approaches to selectively stimulate the ON pathway to treat visual disease.

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**STAR METHODS**

**CONTACT FOR REAGENT AND RESOURCE SHARING**

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Jose-Manuel Alonso (jalonso@sunyopt.edu).

**EXPERIMENTAL MODEL AND SUBJECT DETAILS**

All experiments and procedures were performed in accordance with the guidelines of the United States Department of Agriculture (USDA) and approved by the Institutional Animal Care and Use Committee (IACUC) at the State University of New York, State College of Optometry. Adult male cats (Felis catus, 4–7 kg, n = 13) were housed in groups, provided with enrichment items and fed Purina cat food. They were allowed free roaming time out of their housing, within their private room in the animal facility, during the day and had daily interaction with animal facility personnel. Cats were not allocated to any experimental groups.

**METHOD DETAILS**

**Surgery and preparation**—Adult male cats were tranquilized with an intramuscular injection of acepromazine (0.2 mg kg$^{-1}$) and anesthetized with an intramuscular injection of ketamine (10 mg kg$^{-1}$). One intravenous catheter was inserted into each hind limb to administer continuous infusions of propofol (5–6 mg kg$^{-1}$ h$^{-1}$), sufentanil (10–20 ng kg$^{-1}$ h$^{-1}$), vecuronium bromide (0.2 mg kg$^{-1}$ h$^{-1}$), and saline (1–3 mL h$^{-1}$). The vital signs, including heart rate, blood pressure, electrocardiogram (EKG), temperature, expired CO2, pulse oximetry, and electroencephalogram (EEG), were carefully monitored throughout the surgery/recordings and maintained within normal physiological limits. Once the animal was under continuous anesthesia, the head was carefully secured and a small craniotomy was made over the primary visual cortex. Further details of the surgical procedures have been described previously (Jin et al., 2008; Kremkow et al., 2016).

**Electrophysiological recordings and data acquisition**—Two 32-channel linear multielectrode arrays (0.1 mm inter-electrode distance, Neuronexus) were horizontally introduced in the primary visual cortex (< 5 deg angle relative to the horizontal plane and centered in layer 4) to measure cortical multiunit activity. The recordings were filtered between 250 Hz and 8 kHz, sampled at 40 kHz and collected by a computer running Omniplex (Plexon). The cortical multiunit activity was thresholded at a voltage level of approximately 60 microvolts to record from a restricted population of neurons with each electrode. Throughout the paper, we use the term cortical site when referring to this multiunit cortical activity recorded with a single electrode of the multielectrode probe. The spread of the thresholded cortical multiunit activity is estimated to be 50 microns. Consistently, the response properties of neighboring cortical sites separated by 0.1 mm differ in preference for orientation, direction, receptive field position, geometry, and other spatiotemporal properties (Kremkow et al., 2016). Although there are important differences between individual ON and OFF pathways originating in the retina (Ravi et al., 2018), our paper focuses on the ON and OFF population response generated in visual cortex by
different stimuli, in an attempt to approach more closely a possible correlate with visual psychophysics (Komban et al., 2014; Kremkow et al., 2014; Pons et al., 2017).

**Visual stimuli**—Stimuli were generated with custom MATLAB code (Mathworks) with Psychtoolbox extensions and presented in a gamma corrected 24-inch LCD monitor (BenQ XL2420-B, 120 Hz, mean luminance: 120 cd/m²). In some initial experiments, we used a gamma corrected 21-inch CRT monitor (Sony MultiScan G520, 120 Hz, mean luminance: 35 cd/m²); however, all the data presented and stimuli described below are for the LCD monitor except otherwise specified. The data from the CRT monitor was used only for measurements of spatial receptive fields with sparse noise in Figures 5 and S3, and are shown combined with the data obtained with the LCD monitor. The gamma correction was performed using luminance measures based on the standard V(l) function. The monitor was placed at 0.57 m from the animal.

We mapped the receptive field of each cortical recording site by spike-trigger-averaging sparse noise stimuli made of light (239 cd/m²) and dark (0.27 cd/m²) squares presented on a light (239 cd/m²), dark (0.27 cd/m²), or midgray backgrounds (120 cd/m²). The squares had a side of 2.8 deg and were presented at pseudorandom spatial positions separated by 1.4 deg with an update rate of 30 Hz. The sparse noise stimuli were also used to measure the strength, signal-to-noise, and latency of visual responses. The center of mass of all receptive fields within each recording probe was used to center stimuli for measurements of size and temporal tuning. The summed population receptive field across the 32 electrodes of a multielectrode probe had an average diameter of 10.65 degrees (1.5 times the average receptive field diameter of each cortical recording site, which was 7.1 degrees). The summed population receptive field was aligned with the center of the monitor.

We measured the size and temporal tuning of each cortical recording site with dark (0.27 cd/m²) or light (239 cd/m²) square targets (30–90 repeats) presented with different sizes (1, 4, 7, 11, 14, 17, 20, and 23 deg/side), durations (16, 33, 83, and 133 ms), and background luminances (light/dark or midgray). Each stimulus block contained a sequence of different target sizes with the same polarity, duration, and background luminance. Within this sequence, each target was separated from the next by an interval lasting 150 ms that spanned from the end of one target to the beginning of the next. We also measured the responses of each cortical recording site under different light levels by placing neutral density filters in front of the eye. The neutral density filters reduced the maximum luminance of the stimulus from 239 cd/m² to 0.0239 when using the BenQ LCD monitor, and from 70 cd/m² to 0.007 when using the Sony CRT monitor for data illustrated in Figures 5 and S3.

**Measurements of luminance mesopic range**—To estimate the mesopic luminance range of cats, we measured the visual responses of each cortical recording site to different equiluminant color stimuli presented with different luminances (luminance was reduced by placing neutral density filters in front of the eyes). The photopic (cone-mediated) spectral sensitivity in cats tends to be 550 nm green shifted whereas the scotopic (rod-mediated) spectral sensitivity is ~500 nm blue shifted (Daw and Pearlman, 1969). Therefore, the transition from photopic to mesopic luminance conditions was estimated as the maximum luminance needed to make the green/blue response ratio approach one.
To generate different color stimuli, we first measured the color spectrum of our BenQ monitor to pure red, green, and blue targets (RGB values: [255 0 0], [0 255 0], [0 0 255]). We then generated the spectra for 21 colors and a gray background through a weighted sum of the red, green and blue spectra. For example, the spectra of RGB [0 50 255] was calculated as the green spectra * (50/255) + blue spectra * (255/255). The spectra of each color was multiplied by the corresponding value of the cat photopic spectral sensitivity curve (Saunders et al., 2008). At the end of this process, we obtained the spectra and energy of 21 colors (and gray background) as perceived by the cat eye.

To make all stimuli equiluminant, we first calculated the energy of each color by summing all its spectra values. We then calculated the percentage needed to equalize energy across colors by multiplying the inverse of each color energy (1 / color energy) by the lowest color energy of the spectra (pure red, RGB [255 0 0]). These percentages were then multiplied by the original RGB values for each color to obtain the equiluminant RGB values. The average spectral energy of all colors (0.08 ± 0.001) closely matched the color with the lowest energy (0.07 for pure RGB red [255 0 0]), confirming that all calculated RGB values were equiluminant. The color stimuli consisted of ~10 deg square targets presented in a pseudorandom order for 133 ms with an inter-stimulus interval of 150 ms.

The green/blue response ratio decreased when we reduced the stimulus luminance in both single cortical sites and the average of all cortical sites responsive to color. The cortical responses to green were consistently larger than the cortical responses to blue at high luminance and the green/blue response started to decrease as the stimulus luminance fell below ~12 cd/m². This luminance value is consistent with previous studies estimating a rod-cone break of ~10 cd/m² in cats (Daw and Pearlman, 1969; Shapley and Enroth-Cugell, 1984). At very low light (< 0.6 cd/m²), only dark and light stimuli but not equiluminant color stimuli drove cortical responses (Figure S2C). Therefore, cortical responses to equiluminant color stimuli could only be used to estimate the transition from photopic to mesopic light. Since luminance levels below 0.1 cd/m² do not drive cone pathways in the cat (Daw and Pearlman, 1969; Shapley and Enroth-Cugell, 1984), the mesopic range was estimated to be between 0.1 and 10 cd/m² for all measurements in the paper.

Analysis of image motion stabilization in visual scenes—To test the hypothesis that the ON pathway is better suited for image motion stabilization than the OFF pathway, we stimulated motion jitter in a visual scene and then corrected the jitter using either the light or dark patches of the scene. For this analysis, we used 1,314 calibrated images obtained from the McGill Calibrated Color Image Database (Olmos and Kingdom, 2004) that included flowers, animals, foliage, textures, fruits, landscapes, winter scenes, man-made objects, and shadows.

The images were processed through a simple model with three main stages: retinal, thalamocortical, and image-alignment stage. In the retinal stage, images were converted to grayscale and passed through different ON and OFF luminance/response functions. The luminance response functions were modeled as Naka-Rushton functions using parameters consistent with experimental measures (Kremkow et al., 2014; Pons et al., 2017). The retinal output for each pixel, R(x,y), was determined by the pixel luminance of the original image,
L(x,y), the exponent of the Naka-Rushton function (n), the luminance that generated 50% of the maximum response, L_50, and the maximum response, R_max, as shown in Equation 1. The L_50 and n values were lower for the ON than the OFF pathways to simulate the larger ON than OFF luminance/response saturation that we call neuronal blur (L_50: 0.1, n: 1.6, R_max: 1 for the ON pathway; L_50: 0.5, n: 2.5, R_max: 1 for the OFF pathway).

\[ R(x, y) = R_{max} \frac{L(x, y)^n}{L_50^n + L(x, y)^n} \]  

Equation 1

In the thalamocortical stage, the retinal outputs, Ron (x,y) and Roff (x,y), were convolved with separate difference-of-Gaussians (DoG) functions for ON and OFF pathways, RFon (x,y) and RFoff (x,y), as shown in Equation 2. The results of these convolutions, TCon (x,y) and TCoff (x,y), simulate the filtering of the image by the ON and OFF center-surround receptive fields in retina and thalamus. The center size of the receptive field was 3 pixels for the OFF pathway and 3.4 pixels for the ON pathway to simulate the 14% larger ON than OFF receptive fields (Figure S3). The surround size was 3 times larger than the center for both ON and OFF receptive fields. The surround strength was weaker for ON than OFF receptive fields to simulate the weaker size suppression for ON than OFF pathways (OFF surround strength: 47% of center strength; ON surround strength: 13% of center strength).

\[ T_{Con}(x, y) = Ron(x, y) * RFon(x, y) \]  

\[ T_{Coff}(x, y) = Roff(x, y) * RFoff(x, y) \]  

Equation 2

In the final stage of image alignment, TCon (x,y) and TCoff (x,y) were normalized by their maximum luminance value (divided by maximum pixel value within each image). Then, we selected the pixels with the 10% largest values from TCon (x,y) to make the image of lights and the 10% lowest values from TCoff(x,y) to make the image of darks. The 10% brightest pixels of TCon represent the strongest ON temporal contrast that should drive the strongest ON visual responses during eye movements. The 10% darkest pixels from TCoff represent the strongest OFF temporal contrast that should drive the strongest OFF visual responses. Any negative value in TCoff (x,y) was set to 0, which is the maximum darkest contrast possible. The images of lights and darks were then converted into binary images (MATLAB function ‘im2bw’) and continuous/connected regions of light or dark pixels were identified (MATLAB function ‘bwlabel’) and quantified in number and size. The images of lights and darks were then shifted horizontally by 200 pixels (MATLAB function ‘circshift’) to simulate a change in retinal position during self-motion. Finally, we realigned the images to simulate the eye movement needed to stabilize the image (MATLAB function ‘imreconfig’ for obtaining image configuration, initial radius =0.0001 and maximum iterations = 1, and MATLAB function ‘imregister’ to perform the alignment). The accuracy of the image...
realignement was calculated as the ratio of overlapped pixels between original and realigned images divided by the total number of pixels within the image.

**QUANTIFICATION AND STATISTICAL ANALYSIS**

**Data analysis and selection of cortical recording sites**—Visual responses to all stimuli were quantified from peri-stimulus time histograms (PSTHs) calculated with 1 ms bins and smoothed with a temporal window of 15 ms (MATLAB function 'smooth') separately for each cortical recording site. The PSTHs were then baseline subtracted to limit as much as possible variations in multiunit spontaneous spiking across stimulation conditions, recording sites, and anesthesia levels. The response strength of each cortical recording site was measured as the maximum of the PSTH within a temporal window aligned with the response onset or response rebound. The maximum response onset was measured between 10 ms from the beginning of the stimulus and the end of the response onset. The maximum response rebound was measured between the end of the response onset and 10 ms preceding the end of the inter-stimulus interval. The signal-to-noise ratio was calculated as the ratio between the maximum response onset and the baseline (for response onset), and as the ratio between the maximum response rebound and the baseline (for response rebound). The baseline was defined as the average mean firing rate preceding the response onset.

A cortical recording site was selected for analysis if the signal-to-noise of the response to a 7 deg target (the average receptive field size) was higher than an arbitrary value set to 5. In the analysis of size tuning for response onset, we selected a PSTH series (PSTHs for all stimulus sizes with same stimulus duration from each recording site) if the response onset to a 7 deg target passed the signal-to-noise threshold. This selection process was done independently for stimuli with different polarity (dark or light), different stimulus durations (16, 33, 83, and 133 ms), and different backgrounds (light/dark or midgray). In the analysis of temporal tuning for response onset, we selected a PSTH series (PSTHs for all stimulus durations with same stimulus size from each recording site) if the response onset to a 16 ms target passed the signal-to-noise threshold. The selection of PSTHs for response rebound was similar for size tuning (we selected a PSTH series if the response onset to a 7 deg target passed the signal-to-noise threshold). For temporal tuning, we selected a PSTH series if the response rebound to a 133 ms target passed the signal-to-noise threshold. Any response with a negative value after baseline subtraction was set to zero to calculate the average size tuning and temporal tuning. Because PSTHs with zero baseline could have infinite signal-to-noise, we added a small arbitrary baseline offset to all PSTHs (4 spks/s) to minimize the selection of noisy responses.

To measure the onset/rebound ratio, we selected only PSTHs with both onset and rebound responses that passed the signal-to-noise threshold and divided the maximum onset response by the maximum rebound response. To measure the duration of the response transient, we selected PSTHs with a signal-to-noise larger than 5 and a response larger than 20 spks/s to choose only the strongest, most reliable responses. The response duration was then measured from these PSTHs as the width of the response transient at 20% the amplitude of the response onset. The size suppression was measured from the size tuning as the ratio (Rp-
Rt)/Rp, where Rp is the response at the peak of the tuning and Rt the response at the tail of the tuning. Rp was measured as the maximum response generated by stimulus sizes between 4 and 7 deg and Rt as the minimum response generated by stimulus sizes between 17 and 23 deg. The temporal suppression was measured from the temporal tuning with a similar (Rp-Rt)/Rp ratio. Rp was measured as the maximum response to stimulus durations between 16 and 33 ms and Rt as the response generated by a stimulus duration of 133 ms. In both size and temporal ratios, a positive value indicates suppression and a negative value indicates facilitation. Suppression ratios were calculated independently for darks and lights. For the measurements with neutral density filters, we selected an entire PSTH series (all measurements with neutral-density filters for the same stimulus size or duration) if the PSTH measured with no neutral-density filter passed the signal-to-noise threshold. This selection process was done independently for stimuli with different polarity (dark or light), and different backgrounds (light/dark or midgray).

The signal-to-noise ratio of responses to sparse noise stimuli was calculated before baseline subtraction because the responses were weaker than to other stimuli. Some initial measurements with sparse noise were obtained with a CRT monitor; however, we switched early to an LCD monitor to increase the luminance range of the measurements (239 cd/m\(^2\) for LCD versus 70 cd/m\(^2\) for CRT). The data from the two monitors was combined to measure response strength and the spatial receptive fields. For latency measures, we used data from the LCD monitor only because the two monitors had different temporal responses. The PSTH series measured with sparse noise stimuli across different luminance were selected based on the signal-to-noise ratio obtained before baseline subtraction (1.3 for CRT, 1.5 for LCD). To minimize selecting noise at low light levels, only response latencies that were at least 40 ms long and response amplitudes between 5 and 300 spks/s were included in the analysis. Response latency was calculated as the time to reach the maximum response and the relation between latency and luminance was fit with a linear function.

Receptive field size and receptive field signal-to-noise were measured separately for each cortical recording site from the stimulus spike-trigger-average within 20 ms of the peak response onset. The receptive field size was measured as the number of pixels generating more than 25% of the maximum response and the receptive field diameter calculated as sqrt (2 * pixel count / pi) converted to degrees. The receptive field signal-to-noise was calculated as the maximum value of the receptive field divided by the mean background noise. Only receptive fields with a signal-to-noise larger than 5 (Figures S3E and S3F, left panel) or 10 (Figures S3E and S3F, right panel) were selected. Receptive fields larger than 50 deg were disregarded as noise even if they passed the signal-to-noise criterion because they were all associated with low spike counts and/or near zero baseline. The receptive field selection was done independently for stimuli with different polarity, dark or light, different backgrounds (light/dark or midgray), and luminance condition. For display purposes (Figure S3), receptive fields were thresholded by 25% of the maximum response, interpolated three times (MATLAB function ‘interp2’), and centered at the pixel that generated the maximum response for each luminance condition (MATLAB function ‘circshift’).

In measures of color responses, we selected only cortical recording sites that had robust responses to most color stimuli. Because responses to color were sometimes weak, the
signal-to-noise ratio was also calculated before baseline subtraction as for sparse noise stimuli (signal-to-noise threshold: 1.8 for any color measured without neutral density filters). When a PSTH was selected, all PSTHs for all colors and all neutral density filters for the same cortical site were also selected. Any response value that was negative after baseline subtraction was set to zero in the average. We included 74 cortical sites in the average that showed strong changes in green/blue response ratio as the luminance decreased.

To determine the time course of LCD monitor phosphor activation and deactivation time, a photodiode was placed on the monitor screen and the spatiotemporal tuning stimulus was presented. The photodiode had a rising time of 0.05 ms and a decay time of 0.1 ms. 630 total presentations of dark and light targets (4 – 23 deg) were tested for each duration (16 – 133 ms) and then averaged across all target sizes. The latency of the rise time (time to half-peak) and decay time (time to half-decay) were measured for darks and lights and the difference was calculated.

**Statistical analysis**—All data presented show the mean across multiple stimulus repetitions and cortical recording sites, except in cases of single recording sites that show the mean across multiple stimulus repetitions. All error bars are ± SEM (standard error of the mean) across multiple recording sites, unless specified otherwise. The sample sizes shown in the figure legends indicate the number of cortical recording sites included in the average. All comparisons between darks, lights, target sizes, target durations, and luminance conditions were done using the Wilcoxon RankSum test unless specified otherwise. For comparisons between dark and light receptive field sizes, unpaired Student’s t tests were used as comparing the means rather than medians (Wilcoxon) better represented the receptive field data. We used Chi-square tests to compare the percent reduction in size suppression from photopic to mesopic conditions. This was done because the percent change in each condition were binned with different sample sizes (more than two times the number of mesopic luminance recording sites than photopic luminance recording sites). Chi-square tests were also used for some comparisons in the image analysis. Significance is marked in the figures as follows: * p < 0.05, ** p < 0.01, and *** p < 0.001.

**DATA AND SOFTWARE AVAILABILITY**

Custom code will be provided upon request to upload the published data and generate the figures of the paper (mail to: jalonso@sunyopt.edu).

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Small fast stimuli drive stronger OFF than ON cortical responses.
- Large long-lasting stimuli suppress more OFF than ON cortical responses.
- ON/OFF spatiotemporal asymmetries are preserved across a wide luminance range.
- ON and OFF cortical pathways are specialized in global-slow and local-fast vision.
Figure 1. Cortical Response Preference for Small-Fast Dark Stimuli and Large-Slow Light Stimuli
(A) Example ON and OFF visual cortical responses to dark (blue) and light targets (red) of different sizes (rows) and durations (columns), presented on maximum-contrast backgrounds. The yellow highlight marks the duration of the stimulus. Black arrows point to example OFF responses and gray arrows to example ON responses.
(B) Average cortical responses to the onset of dark (n = 768 recording sites) and light stimuli (n = 780 recording sites) with different sizes (y axis) and durations (x axis). Blue: stronger responses to darks than lights. Red: stronger responses to lights than darks.
(C) Same as (B) but for rebound responses (light off, red, n = 780 recording sites; dark off, blue, n = 762 recording sites).
In the following figures, n indicates the number of recording sites included in each analysis. See also Figure S1.
Figure 2. Pronounced Differences between OFF and ON Size Tuning

(A–D) Size tuning of OFF and ON cortical responses to dark (blue; n = 768) and light (red; n = 780) stimuli presented on maximum-contrast backgrounds for 16 ms (A), 33 ms (B), 83 ms (C), and 133 ms (D).

(E–H) Same as (A)–(D) but for responses on midgray backgrounds (n = 498 for darks; n = 498 for lights).

(I) Average size suppression for OFF and ON cortical responses on maximum-contrast backgrounds. Insets at the top show the distribution of size suppression ratios for 16-ms (left) and 133-ms stimulus presentations (right).

(J) Average size tuning for OFF and ON cortical responses shown separately for each presentation time (left, middle) and averaged across all presentation times (right). Longer durations are illustrated in darker colors.

(K) Same as (J) but for a representative cortical site.

(L–N) Same as (I)–(K) but for midgray backgrounds.
Error bars are standard error of the mean (SEM). *p < 0.05, **p < 0.01, and ***p < 0.001, Wilcoxon rank sum test (same for the following figures unless otherwise specified).
Figure 3. Stronger OFF Than ON Temporal Response Suppression

(A) Stimulus-duration tuning for OFF (blue; n = 654) and ON cortical responses (red; n = 744) on maximum-contrast backgrounds.

(B) Same as (A) but for midgray backgrounds (n = 499 for darks; n = 498 for lights). Notice that the samples are not identical to Figure 2 (e.g., a recording site that responded weakly to brief 16-ms stimuli was included in the stimulus-duration tuning even if it did not pass the significance criteria to be included in the size tuning for 16 ms).

(C) Average temporal suppression for OFF and ON cortical responses on maximum-contrast backgrounds. Insets at the top show the distribution of temporal suppression ratios measured with 4-deg (left) and 23-deg stimuli (right).
(D) Average temporal response onset suppression for each stimulus size (left, middle) and averaged across all sizes (right).
(E) Same as (D) but for a representative cortical site.
(F–H) Same as (C)–(E) but for midgray backgrounds.
Figure 4. Higher OFF Than ON Temporal Contrast Sensitivity and Timing Accuracy
(A) Average rebound responses to different stimulus durations. Notice that ON rebound responses are shown in blue (n = 776) because they are evoked by turning off dark stimuli on light backgrounds and OFF rebound responses are shown in red (n = 773) because they are evoked by turning off light stimuli on dark backgrounds. Rebound responses are shown as the average across all sizes (left) and separately for different stimulus sizes (middle, right).
(B) Same as (A), but for midgray backgrounds (n = 498 for darks; n = 498 for lights).
(C) Size tuning of OFF (light off in red; n = 780) and ON rebound responses (dark off in blue; n = 762) on maximum-contrast backgrounds.
(D) Same as (C) but for midgray backgrounds (n = 496 for darks; n = 498 for lights).
(E and F) Same as (A) and (B) but for the ratio between onset and rebound responses measured on maximum-contrast backgrounds (n = 575 for darks; n = 697 for lights) and midgray backgrounds (n = 495 for darks; n = 498 for lights).
Figure 5. Low Light Affects Similarly the Strength of ON and OFF Cortical Responses

(A) Responses from an OFF-dominated cortical site to dark (blue) and light (red) sparse noise stimuli presented on maximum-contrast backgrounds (left) or midgray backgrounds (right). Responses were measured at multiple stimulus luminances (rows, shaded circles).

(B) Same as (A), but for an ON-dominated cortical site.

(C) Cortical onset response latency (time-to-peak) for dark (blue; n = 332) and light (red; n = 330) sparse noise stimuli presented on maximum-contrast backgrounds and measured at different luminances (left: average across cortical sites; right: example for single cortical site). Equations show the linear fits and goodness-of-fit values (R^2) for darks (blue) and lights (red). The light gray bar denotes the mesopic luminance range.

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(D) Same as (C) but for midgray backgrounds (n = 169 for darks; n = 162 for lights). Error bars (SEM) smaller than the marker size are not shown. Notice that the temporal precision of the LCD monitor is not high enough to measure small latency differences between darks and lights but is good enough to measure the larger latency differences associated with luminance changes.

(E) Average response to darks and lights on maximum-contrast backgrounds for onset responses (left; n = 554 for darks and n = 454 for lights), rebound responses (middle; n = 510 for darks and n = 495 for lights), and total response (onset+rebound). The light gray bar denotes the mesopic luminance range.

(F) Same as (E) but for midgray backgrounds (onset: dark, n = 379; light, n = 343; rebound: dark, n = 355; light, n = 323). See also Figures S2 and S3.
Figure 6. Low Light Affects More ON Than OFF Size Suppression

(A) Size tuning for OFF and ON cortical responses measured on maximum-contrast backgrounds (n = 309 for darks and n = 330 for lights). The responses are averaged across all presentation times under photopic (P), mesopic (M), and scotopic (S) luminances.

(B) Same as (A), but for midgray backgrounds (n = 186 for darks; n = 185 for lights).

(C and D) Same as (A) and (B) but for temporal tuning (n = 293 for darks and n = 338 for lights on maximum-contrast backgrounds; n = 187 for darks and n = 185 for lights on midgray backgrounds).

See also Figures S2, S4, and S5.
Figure 7. Image Stabilization Is More Accurate When Using Light Than Dark Regions of Visual Scenes

(A) Example image passed through separate ON and OFF luminance-response functions (LRFs) and difference-of-Gaussian (DoG) functions and split into an image of darks (darkest pixels, blue) and an image of lights (brightest pixels, red).

(B) Scatterplot illustrating the size of the largest continuous dark and light regions in multiple natural images (left; n = 1,314) and their normalized distribution (right; largest darks in solid blue lines and largest lights in dashed red lines).

(C) Scatterplot illustrating the alignment accuracy (0, completely misaligned; 1, completely aligned) using dark and light image regions. The image alignment is better for darks than lights (higher mean and lower SD).

(D) Scatterplots showing the size of the largest dark and light regions in different image categories.

(E) Same as (D) but for image alignment using darks and lights. Note that some images are included in more than one category so the total number of images across categories is larger than 1,314.

See also Figure S6.
### KEY RESOURCES TABLE

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---------------------|--------|------------|
| **Experimental Models: Organisms/Strains** | | |
| Adult cats, *Felis catus* (4–7 kg) | Liberty Research, Inc., Waverly, New York, USA | N/A |
| **Software and Algorithms** | | |
| MATLAB | MathWorks | R2016a |
| Psychtoolbox-3 | Brainard, 1997 | v3.0.12 |
| **Other** | | |
| Custom 32-channel multielectrode arrays | NeuroNexus | N/A |
| OmniPlex Neural Recording Data Acquisition System | Plexon | N/A |