Current Biology, Vol. 15, 1296–1300, July 26, 2005, ©2005 Elsevier Ltd All rights reserved. DOI 10.1016/j.cub.2005.06.025

Blinking Suppresses the Neural Response to Unchanging Retinal Stimulation

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Summary

Blinks profoundly interrupt visual input but are rarely noticed, perhaps because of blink suppression [1, 2], a visual-sensitivity loss that begins immediately prior to blink onset. Blink suppression is thought to result from an extra-retinal signal that is associated with the blink motor command and may act to attenuate the sensory consequences of the motor action [3–5]. However, the neural mechanisms underlying this phenomenon remain unclear. They are challenging to study because any brain-activity changes resulting from an extra-retinal signal associated with the blink motor command are potentially masked by profound neural-activity changes caused by the retinal-illumination reduction that results from occlusion of the pupil by the eyelid. Here, we distinguished direct top-down effects of blink-associated motor signals on cortical activity from purely mechanical or optical effects of blinking on visual input by combining pupil-independent retinal stimulation with functional MRI (fMRI) in humans. Even though retinal illumination was kept constant during blinks, we found that blinking nevertheless suppressed activity in visual cortex and in areas of parietal and prefrontal cortex previously associated with awareness of environmental change. Our findings demonstrate active top-down modulation of visual processing during blinking, suggesting a possible mechanism by which blinks go unnoticed.

Results

Here, for the first time, we were able to distinguish the direct extra-retinal effects of blinking on cortical activity from the confounding effect of the retinal-stimulation loss caused by eyelid closure. This was achieved by employing a specially designed apparatus to stimulate the retina without light traversing the pupil [1] while brain activity was measured with fMRI. Retinal illumination therefore remained constant irrespective of whether the eyes were open or closed. Despite such constant input to the visual system, blinking strongly reduced activity in both retinotopic visual areas and parietal and prefrontal cortices.

A fiber-optic light source was placed in the mouth of eight individual subjects while we measured their brain activity with fMRI. This apparatus could be used to trans-illuminate (through the palatine bone, which forms the posterior part of the roof of the mouth) both retinas with a flickering light source (see Supplemental Experimental Procedures in the Supplemental Data available with this article online for full apparatus details). Subjects additionally wore opaque light-proof goggles that prevented any light from entering the eye through the pupil. When the oral light source was switched on, retinal stimulation was produced by trans-cranial illumination that was completely unaffected by eyelid closure during blinks. We hypothesized that in such circumstances, any reduction in brain activity associated with blinking would represent a direct neural signature of blinking specifically associated with the blink motor command. Such a reduction would represent a decreased sensitivity to visual stimulation, thus potentially explaining the psychophysical phenomenon of blink suppression and why blinks go unnoticed.

Two factors were independently manipulated in a blocked design to test this hypothesis: the presence (or absence) of retinal illumination via our oral apparatus and the presence (or absence) of voluntary blinking. Because psychophysically measured blink suppression is almost identical for voluntary and involuntary blinking [2, 6], we used a blocked design with a deliberately high frequency of blinks to maximize experimental power to detect any modulation by blinking of the response to the unconventional retinal stimulation. Functional MRI in combination with standard retinotopic mapping procedures [7] and cortical segmentation and flattening [8] was used to functionally identify cortical areas V1–V3 in each individual subject, and the lateral geniculate nucleus (LGN) was localized with standard anatomical and functional criteria [9] (see Supplemental Experimental Procedures for full details). Area V5/MT was localized with a separate motion localizer (see Supplemental Experimental Procedures). Comparison of all conditions in which there was retinal stimulation with those without retinal stimulation confirmed activation of LGN and V1–V3 by our stimulus, but we found no reliable activation of V5/MT. Perhaps V5/MT was not strongly activated by our visual stimulus because it responds best to moving stimuli with high contrast, whereas our stimulus, although flashing, was static and phenomenally relatively diffuse and weak.

Having confirmed that our visual-stimulation device activated retinotopic visual cortex, we next proceeded to characterize the effects of blinking on neural activity in these regions. We also conducted a whole-brain analysis to examine whether visual responses in any areas outside functionally defined retinotopic visual cortex were affected by blinking.

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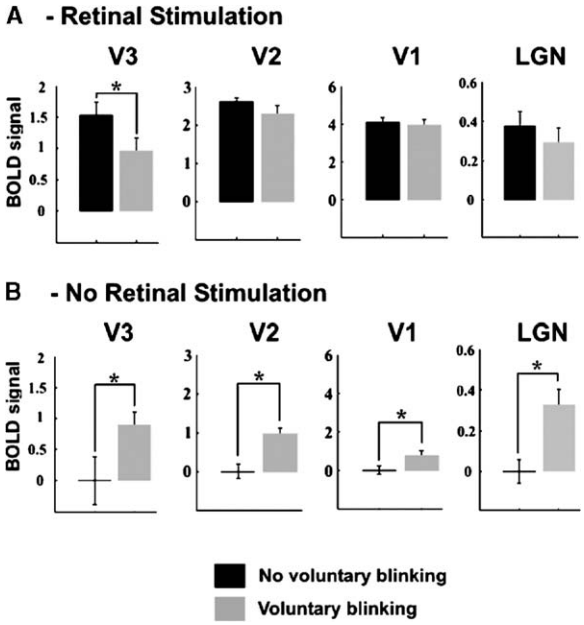

Figure 1. Modulation of Responses in Human Early Visual Cortex by Blinking

(A and B) BOLD contrast responses in human V3, V2, V1, and LGN during no blinking (black) and blinking (gray) conditions in (A) the presence of retinal stimulation through the roof of the mouth and (B) the absence of retinal stimulation. Data are taken from individual retinotopic analyses, and BOLD signal is plotted as a function of condition and averaged across all eight subjects (error bars ± 1 SEM; see Supplemental Experimental Procedures for full details). The asterisk (*) denotes statistical significance ($p < 0.05$) in a two-tailed t test between conditions. (A) V3 shows significantly reduced BOLD signal when blinking in comparison to not blinking during retinal stimulation ($t_{[8]} = 2.974$, $p = 0.018$). Activity in V2 follows the same trend as V3 but does not reach significance ($t_{[8]} = 1.462$, $p = 0.182$). (B) All four retinotopic areas, V3–LGN, show a significant increase in activity during blinking in comparison to no blinking conditions in the dark (V3 $t_{[8]} = -5.501$, $p = 0.001$; V2 $t_{[8]} = -5.454$, $p = 0.001$; V1 $t_{[8]} = 3.422$, $p = 0.009$; and LGN $t_{[8]} = -4.533$, $p = 0.015$).

Retinotopic Analysis

In the presence of retinal stimulation, activity was strongly and significantly reduced by blinking in retinotopic area V3 ($t_{[8]} = 2.974$, $p = 0.018$) (see Figure 1A). Thus, even when input to the visual system is held constant, blinks can modulate activity in retinotopic visual areas. Blinking also reduced activity during retinal stimulation in LGN and V2, but this difference did not reach statistical significance (LGN $t_{[8]} = 1.036$, $p = 0.335$; V2 $t_{[8]} = 1.462$, $p = 0.182$) (see Figure 1A). In V1, there was no significant difference between blinking and no blinking in the presence of visual stimulation ($t_{[8]} = 0.642$, $p = 0.539$).

In the absence of retinal stimulation, a different pattern of responses to blinks emerged. In contrast to the reductions in activity associated with blinking in the presence of retinal stimulation, blinking (compared to no blinking) in the absence of retinal stimulation significantly *increased* activation in both LGN ($t_{[8]} = -4.533$, $p = 0.003$) and retinotopic areas V1 ($t_{[8]} = -3.422$, $p = 0.009$), V2 ($t_{[8]} = -5.454$, $p = 0.001$), and V3 ($t_{[8]} = -5.501$, $p = 0.001$) (see Figure 1B). The effects of blinking therefore differed in the presence and absence of retinal stimulation. Whereas blinking strongly suppressed the response to retinal stimulation in retinotopic area V3, in the absence of any retinal stimulation blinking resulted in an enhanced signal in early cortical areas and the LGN.

Whole-Brain Analysis

To determine whether the neural responses to retinal stimulation in any brain regions outside the functionally defined retinotopic visual areas considered above were also affected by blinking, we conducted an unrestricted whole-brain analysis. When retinal stimulation was present, there were highly significant ($p < 0.05$ false discovery rate [FDR] corrected) reductions in activity during blinking (versus no blinking) in several regions of parietal and prefrontal cortices (see Figure 2; see Table 1 for full list of loci), mainly in the right hemisphere. The locations of these parietal and prefrontal regions, which were suppressed by blinking, were clearly spatially distinct from oculomotor structures such as the supplementary and frontal eye fields [10–13], which were strongly activated by the reverse comparison of blinking versus no blinking conditions collapsed across retinal illumination conditions (see Figure 2; see Table S1 for full list of loci). Nonoculomotor regions of parietal and prefrontal cortex therefore show a reduction in activity during blinking in the presence of retinal stimulation.

Discussion

The neural mechanisms underlying blink suppression have always been challenging to study because of the confounding effects of the visual-input loss caused by eyelid closure; these effects potentially mask any direct extra-retinal effects of blinking on brain activity. For example, activity of single neurons in monkey early visual areas V1, V2, V3V, and V4V decreases during blinks, demonstrating that visual continuity across blinks does not depend on the maintenance of continuous neural activity in early visual cortex [14, 15]. However, these reductions in activity may simply result from the dramatic loss of retinal illumination associated with eyelid closure during blinks, rather than reflecting an active top-down suppression of visual cortical activity. External darkenings of the entire scene also result in a decrease in neuronal activity in all these early visual areas [14], although in V1 the rate of decay of average activity is slightly slower, and the overall reduction is smaller than during blinks, suggesting that some degree of top-down suppression may occur during blinks [15].

Here, we successfully dissociated the extra-retinal effects of blinking on neural activity from its mechanical or optical effects, and we have demonstrated active suppression of neuronal activity during blinking, despite continuous visual input. We observed a strong and highly significant V3-activity reduction that was associated with blinking (versus no blinking) in the presence of retinal stimulation. This represents a reduction in sensitivity to visual stimulation in this region during blinks and, thus, could represent a neural mechanism

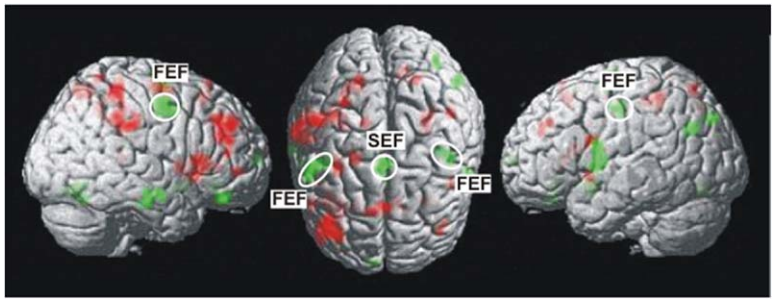

Figure 2. Parietal and Prefrontal Cortices Showed a Reduced Response to Retinal Stimulation when Blinking

Left lateral, right lateral, and superior views of a standard T1 weighted image rendered in the standard space defined by the Montreal Neurological Institute template, with loci showing reduced responses to retinal stimulation when blinking in comparison to not blinking shown superimposed in red on the rendered images ($p < 0.001$ uncorrected and spatial extent threshold of 5 voxels for display purposes). Note the more extensive distribution of such regions in the right hemisphere. Oculomotor regions showing greater activation when blinking in comparison to no blinking, across retinal-stimulation conditions, are shown superimposed in green on the rendered images ($p < 0.05$ FDR-corrected and spatial extent threshold of 5 voxels for display purposes). The main oculomotor regions controlling blinking, that is, the frontal eye-fields (FEF) and supplementary eye-field (SEF), are labeled (see Table S1 for full list of loci). Note the lack of overlap between these oculomotor structures (in green) and the regions suppressed by blinking (in red).

underlying the psychophysical phenomenon of blink suppression. Blinking did not significantly affect responses to retinal stimulation in the LGN and cortical areas V1 and V2. Therefore, it appears that, as in monkeys, activity in LGN, V1, and V2 may reflect visual input during blinks (which here remained continuous) [14], and any extraretinal modulation of visually evoked activity in these areas is modest [15]. However, note that a positive signal was consistently observed in association with blinking in darkness in these areas. This may represent a motor signal that, if also present during retinal stimulation, could lead to underestimation of any direct suppressive effect of blinks on sensory processing.

Whereas it might have been supposed that blink suppression is a purely low-level visual phenomenon, mediated solely by retinotopic visual areas, our whole-brain analysis surprisingly revealed that activity evoked by retinal stimulation in parietal and frontal cortices was also suppressed by blinking (see Figure 2). These regions cannot merely be responding to a change in retinal illumination because retinal illumination was not affected by eyelid closure during blinks. Our special stimulation apparatus and the use of opaque goggles ensured that retinal illumination remained constant whether the eyes were open or closed. The reduction in activity seen during blinks is therefore likely to be related to an extra-retinal neural signal associated with the blink motor command from the nonoverlapping oculomotor regions (see Figure 2; see Table S1 for full list of loci). Activation of parietal and prefrontal cortices has been consistently associated with fluctuations in the contents of consciousness, for example as occurs during binocular rivalry [16], when viewing ambiguous figures [17], or during conscious detection of changes in the visual scene [18]. Loci activated in those studies have similar spatial locations to those demonstrating suppressed activity when blinking in the present study.

Table 1. Cortical Loci where Voluntary Blinking Reduced Activity Associated with Retinal Stimulation

	x	y	z	Z	*p-corr (FDR)*
Right inferior frontal sulcus	42	36	27	5.08	0.006
Right inferior frontal gyrus	48	6	3	3.81	0.045
Left inferior frontal gyrus	−48	6	21	4.20	0.028
Right cingulate sulcus	0	24	54	4.90	0.009
Right superior frontal gyrus	9	27	63	4.82	0.010
Right head of caudate nucleus	21	24	6	4.72	0.013
Left head of caudate nucleus	−12	27	9	3.97	0.035
Right putamen/internal capsule	18	12	3	4.25	0.026
Right insula	33	27	6	4.56	0.019
Left short insular gyri	−39	6	−6	4.31	0.024
Left circular insular sulcus	−30	18	15	3.76	0.048
Right precentral gyrus	15	−36	63	4.52	0.019
Right precentral sulcus	33	−3	60	4.09	0.035
Right superior precentral sulcus	21	−12	60	4.46	0.019
Right postcentral gyrus	30	−36	45	4.03	0.035
Left postcentral gyrus	−30	−42	54	3.94	0.035
Right superior parietal gyrus/IPS	21	−69	57	4.43	0.020
Left superior parietal gyrus/IPS	−21	−66	60	3.70	0.050
Right intraparietal sulcus	30	−51	42	3.95	0.035
Right angular gyrus/IPS	57	−39	39	4.33	0.023
Right supramarginal gyrus	63	−30	33	4.11	0.035

Shown in the table are the locations, stereotactic coordinates in the space defined by the Montreal Neurological Institute template, Z scores, and corresponding p value (corrected for multiple comparisons across the volume examined). A statistical threshold of $p < 0.05$, corrected for multiple comparisons across the entire brain volume, and a spatial extent threshold of 5 voxels, was used.

Thus, one possible interpretation of our findings is that the observed *suppression* of these parietal and prefrontal regions during blinking represents a neural mechanism underlying the *lack* of awareness of the changes in visual input that normally occur during a blink. Specifically, it may account for the lack of awareness of the percept of the eyelid descending across the pupil and the resulting reduction in retinal illumination.

In contrast to the suppression of activity during retinal stimulation by blinks in both retinotopic V3 and parietal and prefrontal cortices, we also observed, in the LGN and early visual areas V1–V3, a positive signal associated with blinking in the absence of retinal stimulation (Figure 1B). Because retinal stimulation was entirely absent in these particular conditions, we propose that these activations represent a motor signal associated with blinking in visual cortex. This finding replicates earlier, and often unremarked, findings of visual cortex activation in darkness during blinking (e.g., Figure 4 of [11]) in studies that have focused primarily on frontal oculomotor control structures [10–12, 19]. These observations, plus the here-demonstrated contextual dependence of blink-associated signals on retinal illumination, run strikingly parallel to recent observations of a similar dependence of saccadic responses in these brain areas on the presence (or absence) of retinal stimulation [20]. When saccades are made in the dark, a positive (motor) signal is seen in LGN and V1, whereas during retinal illumination, saccades result in a reduction in visually evoked activity in these areas. Taken together, these findings may represent some preliminary evidence that blink suppression and saccadic suppression share some common neural mechanisms, as previously predicted on purely theoretical grounds [2, 21]. Indeed, although any eye movements during a blink are very small [22–24], blinks themselves can change the kinematic properties of horizontal saccades [25], suggesting that the motor signals associated with blinking and the saccadic premotor circuit can interact. Currently, there is good physiological evidence in monkeys for the existence of a corollary discharge pathway from the superior colliculus to the frontal eye-fields (FEF), during saccades, which may serve to coordinate sequential saccades and stabilize vision across saccades [26–28]. We speculate that a similar corollary discharge pathway may operate during blinks to attenuate their sensory consequences.

In summary, our data demonstrate that responses to retinal illumination are suppressed by blinking in retinotopic visual area V3 and in parietal and prefrontal cortices, whereas in the absence of retinal stimulation, we identified a positive blink-related signal in early visual areas LGN–V3. We propose that these findings represent a neural signature of blinking associated with the blink motor command and may go some way toward explaining both the neural mechanisms underlying the visual-sensitivity loss, known as blink suppression, that occurs during blinks, and why they go unnoticed. Our findings parallel recent observations of saccade-related changes in activity in visual cortex during saccades, suggesting that blink suppression and saccadic suppression may indeed share common neural mechanisms. However, the precise neural mechanisms relating the blink motor command to the neural suppression that we observed here remain to be explored.

Supplemental Data

Detailed Experimental Procedures and a supplemental table are available at http://www.current-biology.com/cgi/content/full/15/14/1296/DC1/.

Acknowledgments

The Wellcome Trust funded this work. We thank Peter Aston and Eric Featherstone for their help building the retinal illumination apparatus and ensuring its MRI compatibility.

Received: April 27, 2005
Revised: June 5, 2005
Accepted: June 6, 2005
Published: July 26, 2005

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