Eyeblinks are defined as a rapid closing and opening of the eyelid. Three types of blinks are classically defined: spontaneous, reflexive, and voluntary. Here, we focus on the cortical correlates of spontaneous blinks, using functional magnetic resonance imaging (fMRI) in the nonhuman primate. Our observations reveal an ensemble of cortical regions processing the somatosensory, proprioceptive, peripheral visual, and possibly nociceptive consequences of blinks. These observations indicate that spontaneous blinks have consequences on the brain beyond the visual cortex, possibly contaminating fMRI protocols that generate in the participants heterogeneous blink behaviors. This is especially the case when these protocols induce (nonunusual) eye fatigue and corneal dryness due to demanding fixation requirements, as is the case here. Importantly, no blink related activations were observed in the preretal and parietal blinks motor command areas nor in the prefrontal, parietal, and medial temporal blink suppression areas. This indicates that the absence of activation in these areas is not a signature of the absence of blink contamination in the data. While these observations increase our understanding of the neural bases of spontaneous blinks, they also strongly call for new criteria to identify whether fMRI recordings are contaminated by a heterogeneous blink behavior or not.

**Keywords:** blink, eye fields, fMRI, macaque, spontaneous

**Introduction**

Eyeblinks are defined as a rapid closing and opening of the eyelid. Three types of blinks are classically defined. *Spontaneous blinks* play an important role in the protection of the eye conjunctiva and the underlying cornea from dehydration, by regenerating the tear film over successive eyelid closures (Korb et al. 1994). *Reflexive blinks* are a defensive behavior to a situation of threat involving the head (Miwa et al. 1996; Valls-Sole et al. 1997; León et al. 2011). These blinks achieve the protection of the eyes by the eyelids and are often associated with other protective behaviors such as head and trunk withdrawal movements. *Voluntary blinks* are under the control of volition (Bristow, Frith, et al. 2005; Hanakawa et al. 2008). Such blinks can be used during nonverbal communication. They can also be generated to protect the eyes voluntarily (e.g., protect the eyes from the sun, increase the tear film in order to get rid of a foreign body such as an insect or sand dust). These different types of blinks appear to involve different neuronal substrates. For example, at the peripheral level, voluntary blinks activate a specific class of eyelid motor units that are not activated by any of the other types of eyeblinks (Gordon 1951). Likewise, bilateral voluntary blinks involve a specific rotation of the eye globe, known as the Bell’s phenomenon (Collewijn et al. 1985). Differences can also be observed at the central level. Indeed, patients suffering from apraxia retain the ability to produce spontaneous blinks while they are profoundly impaired in the generation of voluntary eyeblinks (Colombo et al. 1982; van Koningsbruggen et al. 2012).

A majority of the studies on the neurophysiological substrates of blinks has focused on voluntary eyeblinks (Bodis-Wollner et al. 1999; Kato and Miyachi 2003a, 2003b; Bristow, Frith, et al. 2005; Hanakawa et al. 2008; van Koningsbruggen et al. 2012). The few reports that have sought a direct comparison of the physiological tenants of the different types of eyeblinks highlight interesting differences. In particular the parieto-frontal regions involved in oculomotor behavior, namely the frontal eye fields (FEF) and the lateral intraparietal area (LIP), are reliably activated during voluntary eye blinks and not during spontaneous eye blinks (Gordon 1951; Colombo et al. 1982; Collewijn et al. 1985; van Koningsbruggen et al. 2012). Apart from this consensus, the reported blink-related regions vary from one study to another, most probably due to experimental and analysis specificities.

Here, we describe, using functional magnetic resonance imaging (fMRI) in the nonhuman primate, the cortical regions that are activated by spontaneous blink production. Our observations, discussed in the light of the numerous anatomical and connectivity studies available for this species, reveal an ensemble of cortical eye fields involved in the representation of the somatosensory, proprioceptive, visual, and possibly nociceptive correlates of blinks. Specifically, we describe a core somatosensory network involving the area 2, area 3a/3b, and area secondary somatosensory cortex (SII)/parietoventral cortex (PV) eye fields, a larger network involving parietal median intraparietal area (MIP), cingulate (caudal cingulate eye field, CEFc), insular (parainsula) and promotor area (ProM), as well as striate and extrastriate regions (visual area V1 (V1), visual area V2 (V2), and medial superior temporal area (MST)). Interestingly, we describe, in a unique study, the several spontaneous blink-related regions reported disparately in several human imaging studies, thus providing a unified description of the cortical spontaneous blink correlates, though some of our observations might be directly related to the specific (non-unusual in fMRI studies) fixation requirements of the task possibly inducing corneal and eye strain/pain.

**Material and Methods**

**Subjects and Materials**

Two rhesus monkeys (female M1, male M2, 5–7 years old, 5–7 kg) participated in the study. The animals were implanted with a plastic magnetic resonance imaging (MRI) compatible headset covered by dental acrylic. The anesthesia during surgery was induced by Zoletil (Tiletamine–Zolazepam, Virbac, 5 mg/kg) and followed by Isoflurane (Bela- mont, 1–2%). Postsurgery analgesia was ensured thanks to Temgesic (buprenorphine, 0.3 mg/ml, 0.01 mg/kg). During recovery, proper analgesic and antibiotic coverage were provided. The surgical procedures
conformed to European, and National Institutes of Health guidelines for the care and use of laboratory animals.

During the scanning sessions, monkeys sat in a sphinx position in a plastic monkey chair positioned within a horizontal magnet (1.5-T MR scanner Sonata; Siemens, Erlangen, Germany) facing a translucent screen placed 90 cm from the eyes. Their head was restrained and equipped with MRI-compatible headphones customized for monkeys (MR Confon GmbH, Magdeburg, Germany). A radial receive-only surface coil (10-cm diameter) was positioned above the head. Eye position was monitored at 120 Hz during scanning using a pupil-corneal reflection tracking system (Iscan®), Cambridge, MA). Monkeys were rewarded with liquid dispensed by a computer-controlled reward delivery system (Crist®) thanks to a plastic tube close to their mouth. The task, all the behavioral parameters as well as the sensory stimulations were controlled by 2 computers running with Matlab® and Presentation®. The fixation point the monkeys were instructed to fixate was projected onto a screen with a Canon XEED SX60 projector. Auditory stimulations were dispensed with a MR Confon GmbH system (Magdeburg, Germany). Tactile stimulations were delivered through Teflon tubing and 6 articulated plastic arms connected to distant air pressure electro-valves. Monkeys were trained in a mock scan environment approaching to the best the actual MRI scanner setup.

**Task and Stimuli**

The animals were trained to maintain fixation on a red central spot (0.24° × 0.24°) while stimulations (auditory, or tactile) were delivered. The monkeys were rewarded for staying within a 2° × 2° tolerance window centered on the fixation spot. The reward delivery was scheduled to encourage long fixation without breaks (i.e., the interval between successive deliveries was decreased and their amount was increased, up to a fixed limit, as long as the eyes did not leave the window). The 2 sensory modalities were tested in independent interleaved runs (see below for the organization of the runs).

**Auditory Stimulations**

In both monkeys, we used coherent movement, scrambled and static auditory stimuli. Scrambled stimulations were obtained by cutting the movement sounds in 100 or 300 ms segments and randomly mixing them. Static stimulations consisted of auditory stimuli evoking a stable stimulus in space (details are provided in Guipponi et al. 2013).

**Tactile Stimulations**

They consisted in air puffs delivered to 3 different locations on the left and the right of the animals’ body: (1) center of the face, close to the nose and the mouth; (2) periphery of the face, above the eyebrows; (3) shoulders (cf. Guipponi et al. 2013).

Functional time series (runs) were organized as follows: a 10-volume block of pure fixation (baseline) was followed by a 10-volume block of category 1 stimulus type, a 10-volume block of category 2 stimulus type, and a 10-volume block of category 3 stimulus type; this sequence was played 4 times, resulting in a 160-volume run. The blocks for the 3 categories were presented in 6 counterbalanced possible orders. A retinotopy localizer was run independently in the 2 monkeys using exactly the stimulations of Fize et al. (2003). This localizer is used to localize the central and peripheral representations of visual areas within each hemisphere, in both animals.

**Scanning**

Before each scanning session, a contrast agent, monocryalline iron oxide nanoparticle (Sinerem, Guerbet or Feraheme, AMAG, Vandeluff et al. 2001), was injected into the animal’s femoral/saphenous vein (4–10 mg/kg). For the sake of clarity, the polarity of the contrast agent MR signal changes, which are negative for increased blood volumes, was inverted. We acquired gradient-echo echoplanar (EPI) images covering the whole brain (1.5 T; repetition time (TR) 2.08 s; echo time (TE) 27 ms; 32 sagittal slices; 2 × 2 × 2-mm voxels). During each scanning session, the runs of different modalities and different orders were pseudorandomly intermixed. A total of 37 (42) runs was acquired for auditory stimulations in M1 (M2) and 36 (40) runs for tactile stimulations.

**Analysis**

A total of 25 (31) runs were selected for the auditory stimulation condition in M1 (M2), 18 (28) for the tactile stimulation condition and 20 (24) for the retinotopy localizer based on the quality of the monkeys’ fixation throughout each run (>85% within the tolerance window). Time series were analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). For spatial preprocessing, functional volumes were first realigned and rigidly coregistered with the anatomy of each individual monkey (T1-weighted MPRAGE 3D 0.6 × 0.6 × 0.6 mm or 0.5 × 0.5 × 0.5 mm voxel acquired at 1.5 T) in stereotactic space. The JIP program (Mandeville et al. 2011) was used to perform a nonrigid coregistration (warping) of a mean functional image onto the individual anatomies. For each run and each animal, we extracted the timings of the blink events as follows. Blinks correspond to a stereotyped closure of the eye lids. During this interval, the tracking of the pupil by the video eye-tracker is disrupted, resulting in a saturation of the eye signal (Fig. 1A,C). The duration of the eye blinks varies from one subject to another (VanderWerf et al. 2003). Here, we defined eye blink events as follows. We calculated the duration of all conjugate eye signal saturation events (i.e., taking place on both vertical and horizontal eye signals simultaneously). The distribution of the duration of these saturation events are presented in Figure 24 for monkeys M1 and M2. Each distribution is characterized by a core set of events corresponding to blink events, prolonged by a tail, corresponding to other types of saturation events (rest, sleep, saccades beyond 25° of eccentricity), possibly associated with some long duration blink events. The tail is not extremely marked because the fMRI analysis was performed on the acquisition runs in which the monkeys achieved over 85% correct fixation.

![Figure 1](image-url)  
**Figure 1.** Extraction of eye-blink events and resulting theoretical convoluted signal. (A) Vertical eye position recorded over time. The trace presented has been extracted from a single run. Sharp transient drops of the signal characterize blink events. The red dashed-line box represents the 2° fixation window the monkeys are rewarded to stay in. Signal outside this window is identified as fixation breakdown and referred to either saccades or blinks depending on the amplitudes and durations of these events. (B) Blink-related convoluted signal. The temporal occurrence of the blink events are convoluted with the appropriate hemodynamic response function (see Material and Methods for more details). In this figure, the resulting signal has been temporally aligned with the vertical eye trace. (C) Close-up of vertical eye position and the resulting convoluted signal extracted from Figure 1(A, B) (black rectangles). A high blink event frequency is associated with an increase in the convoluted response function.
For both monkeys, a cutoff is applied at 225 ms to remove this tail and exclude those events that depart from the average eye saturation events. This leads to the exclusion of 3.3% of eye saturation events in monkey M1 (3.2% in monkey M2, respectively). Because eye saturation events were conjugated across x and y eye signals, the analysis yielded the same results whether performed on the vertical or on the horizontal eye signals.

These blink events were then convolved with the appropriate hemodynamic response function (i.e., evoked by dextran-coated iron oxide agents, monocryalline iron oxide nanocompound (MION); Fig.1B) and the output of this operation was used as a regressor. Results are displayed on individual flattened maps obtained with Caret (Van Essen et al. 2001; http://www.nitrc.org/projects/caret/). The results are shown both at $P < 0.05$ corrected for multiple comparisons (FEW, $t > 4.89$) and $P < 0.001$ uncorrected level. We also extracted the interblink intervals (IBI) for each monkey and each run (Fig. 2B).

When coordinates are provided, they are expressed with respect to the anterior commissure.

Kruskal–Wallis Test
A one-way Kruskal–Wallis test was performed in order to investigate whether the different conditions within a given run evoked statistically significant, different number of blinks. This analysis was also used to test whether (1) the auditory and the tactile conditions result in a different number of blinks and (2) the blink events were statistically different across animals. Whenever the Kruskal–Wallis null hypothesis was rejected, a Mann–Whitney post hoc test was further used to specify the conditions in which blink generation was most affected.

Results
The results specifically identify spontaneous (as opposed to reflexive or voluntary) blink-related cortical activations. In a first section, we analyze the monkeys’ blinking behavior. We then report the cortical sites which are reliably activated by eye blinks, both during auditory and tactile stimulation runs.

Behavioral Analysis
For each monkey and each run, we extracted the timestamps at which eye blinks were produced. These blink events can easily be identified from the eye traces as short duration signal saturation periods due to the occlusion of the pupil as can be seen in Figure 1A and the corresponding close-up in Figure 1C. Signal saturation periods appear as sharp transient drops in the eye trace. The duration of the eye blinks varies from one subject to another (VanderWerf et al. 2003). The eye blinks of monkey M1 lasted <100 ms while monkey M2 had longer blinks (upper duration threshold of 200 ms). These blink events are clearly distinct from saccades which result in smaller amplitude changes in the eye traces compared with the blinks. They are also clearly distinct from eye closed resting or sleeping periods which last significantly longer. In the following, we consider only the runs during which the monkey achieved fixation for >85% of the entire duration of the run. This allows...
to minimize the potential noise induced by eye movement and resting periods.

Monkey M1 produced an average of 17.5 (median: 16.6) blinks min\(^{-1}\), while monkey M2 had a mean blink rate of 7.3 (median: 6.5) blinks min\(^{-1}\) (Kruskall–Wallis test, \(P<0.0001\), Table 1). The corresponding IBI are represented in Figure 2B for monkey M1 (mean = 3.4, median = 2.1) and monkey M2 (mean = 8.2, median = 7.2). These IBI distributions are not Gaussian (Kolmogorov–Smirnov test, monkeys M1 and M2, \(P<10^{-14}\)), indicating that blink generation is produced by a nonGaussian process.

Monkey M1 produced significantly more eye blinks during the auditory runs (mean: 18.7 blinks min\(^{-1}\), median: 18.4) than during the tactile runs (mean: 15.9 blinks min\(^{-1}\), median: 14.4, \(P<0.05\)). In monkey M2 this difference was not significant (tactile runs, 8.0 blinks min\(^{-1}\), median: 6.5, auditory runs, 6.8 blinks min\(^{-1}\), median: 6.5, Kruskal–Wallis test, \(P=0.09\)).

Within a given sensory stimulation run, stimulations varied in block. Auditory stimulations could be present or absent (fixation baseline condition). When present, they could thus either elicit the percepts of static auditory source (static condition), the percept of a moving source around the head (movement condition) or the percept of a random spatial nonlocalized auditory source (scrambled condition, see Guipponi et al. 2013 for details). Similarly, tactile stimulations could be present or absent (fixation baseline condition). When present, they could be directed either to the center of the face, to the periphery of the face or else to the shoulders (Guipponi et al. 2013). Auditory stimulation conditions did not affect blink rate in either monkeys (Kruskal–Wallis test, auditory stimulation condition main factor, monkey M1, \(P<0.50\), monkey M2, \(P<0.77\), Table 1). These different conditions could thus be considered as evolving only spontaneous blinks in both monkeys. Tactile stimulation conditions did not affect blink rate in monkey M1 (Kruskal–Wallis test, tactile stimulation condition main factor, monkey M1, \(P<0.12\)). In contrast, the blink rate of monkey M2 was strongly dependent upon the tactile stimulation condition (\(P<0.0001\)). Post hoc Mann–Whitney tests reveal that the Center of the face condition evoked a higher number of blinks compared with the 3 other tactile conditions (Periphery of the face condition, \(P<0.002\), Shoulder condition, \(P<0.001\); fixation baseline condition, \(P<0.0003\), Table 1). In this Center of the face condition, both spontaneous and reflexive blinks thus seemed to be evoked, at least in monkey M2 (see also Discussion).

**Functional Analysis**

In order to identify the cortical correlates of spontaneous eye blinks, we performed a conjunction analysis for both the auditory and the tactile blink regression analyses. This conjunction analysis allows us to identify blink-related activations that are independent from the sensory conditions and that correlate with the blink pattern common to both conditions, i.e., spontaneous eye blinks. The blink events were convoluted with the appropriate hemodynamic response function (evoked by dextran-coated iron oxide agents, MION, Vanduffel et al. 2001). The resulting signal (Fig. 1B,C, lower part) was used as a regressor for the whole brain analysis. The outcome of this analysis is presented for each individual monkey (uncorrected level, \(P<0.001\), Fig. 3). Table 2 provides a detailed description of the localization (coordinates with respect to the anterior commissure) and t-scores of the obtained activations. Activations are considered as robust when identified in both monkeys and in at least 3 out of the 4 hemispheres.

Eye blinks activated somatosensory area 2, at the anterior tip of the intraparietal sulcus (3 hemispheres out of 4); somatosensory areas 3a and 3b, on the anterior and posterior banks as well as in the fundus of the central sulcus (all 4 hemispheres); the somatosensory complex SII/PV (all 4 hemispheres). The bilateral somatosensory areas 3a/3b and SII/PV activations are represented on the corresponding coronal section of both monkeys in Figure 4 (see Supplementary material, Localization of central sulcus activations, for an in depth description of the 3a/3b activation localization). Blink-related activations were found in somatosensory area 1 in only one hemisphere out of 4 (in the right hemisphere of monkey M1) and are thus considered as less reliable. Activations were also found in somatosensory parainsular area parainsular cortex (PI) (also known as the disgranular insular cortex, Id). Anterior to PI, the activity of ProM, a subdivision of the frontal opercular region PrCo highly correlated with spontaneous eye-blink production in all 4 hemispheres while prefrontal area ventral premotor area 6Vb (6Vb) was found to be responsive to blinks only in monkey M1 (both hemispheres). Parietal activations were found in medial parietal area MIP in all hemispheres. Medially, blinks activated a posterior region close to V1, identified as area PG, medial area (PGm) (3 hemispheres out of 4), and an anterior region above the anterior cingulate sulcus, identified as cingulate area 24d (24d) (in all hemispheres). In addition, monkey M1 presented a blink-related activation in 2 symmetrical locations on the convexity above the ascending posterior branch of the central sulcus of each hemisphere, as well as a bilateral activation on the upper bank at the anterior tip of the cingulate cortex, identified as cingulate area 24c (24c) (also present in one hemisphere in monkey M2). An orbitofrontal blink-related response was also observed in the left hemisphere of monkey M2, in a region corresponding to areas 11 and 13.

Reliable blink-related activations were finally observed in early striate and extrastriate areas: in V1 (all 4 hemispheres), in the visual area V2, ventral part (V2v) (all 4 hemispheres), and in visual area V3 (V3)-visual area V3A (V3A) and visual area V2, dorsal part (V2d), specifically in monkey M1, bilaterally. In monkey M1, this V3-V3A activation at the junction of the lunate

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**Table 1**

<table>
<thead>
<tr>
<th>All</th>
<th>Auditory</th>
<th>Tactile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Mvt</td>
</tr>
<tr>
<td>M1</td>
<td>17.5/16.6</td>
<td>18.7/18.4</td>
</tr>
<tr>
<td>M2</td>
<td>7.3/8.5</td>
<td>6.8/6.5</td>
</tr>
</tbody>
</table>

Mvt, moving auditory stimuli; Scramb, scrambled auditory stimuli; Static, static auditory stimuli; Center, center of the face tactile stimuli; Periph, periphery of the face tactile stimuli; Shld, shoulder tactile stimuli; Fix, fixation condition with no sensory stimulation.
and the intraparietal sulci, potentially extends, in both hemispheres into posterior intraparietal area. Remarkably, all these striate and extra-striate activations fell exclusively within the peripheral visual field representation (Fig. 5, blue regions), as defined by standard retinotopic localizers (Fize et al. 2003).

**Discussion**

In the present study, we describe the whole brain cortical activations correlating with nonvoluntary eyeblinks as measured in a fixation task during which the monkeys received either auditory stimulations or tactile stimulations to the face.
**Blink-Related Behavior in the Active Monkey**

Interindividual variability in blink rate is well documented in both humans and nonhuman primates and appears to be under the dependence of dopaminergic regulation (Karsen 1983; Taylor et al. 1999). A recent study by Tada et al. (2013) systematically explores eye-blink behavior in 71 nonhuman primate species. Interestingly, the blink rates we report here fall within the range of variability the authors describe for macaque monkeys (mean = 14.5 blinks min⁻¹, SD = 5.3).

As described in the Introduction, blinks can be voluntary, reflexive, or spontaneous. The blinks produced by the 2 monkeys during the fixation task they are required to perform are supposedly nonvoluntary. Our results mainly describe spontaneous blinks neural correlates. However, this requires further consideration. The blinks produced during the auditory stimulation context (auditory runs) can be considered as essentially spontaneous. Indeed, the auditory stimuli were designed to elicit a nonthreatening percep of a dynamic sound moving in the peri-personal space around the head, and the monkeys did not show any difficulty at maintaining fixation in such a context. In contrast, the blinks produced during the tactile stimulation context (tactile runs) consist in a mixture of spontaneous and reflexive eye blinks. This was particularly clear when the air-puff tactile stimulations were initially introduced during the training phase. This correlated with a drastic drop in the fixation performance and a high correlation between blinking events and tactile stimulation events. Monkeys progressively habituated to the air-puffs and fixation performance increased back to our run selection criteria (fixation maintained during 85% of the run duration or more, see Materials and Methods). This habituation also correlated with a decrease in blink rates back to the spontaneous blinking rate for periphery of the face and shoulder stimulation conditions, as described in the Results. Air-puffs to the center of the face, directed to the sensitive skin on each side of the snout, still induced more eye blinks than all other conditions. This sensory condition can thus be considered to elicit both spontaneous and reflexive eye blinks. As a result, though the majority of the blinks produced by the monkeys are spontaneous blinks, a small proportion corresponds to reflexive blinks.

**Analysis and Potential Confounds**

The functional description presented here is based on a conjunction analysis describing the blink-related cortical activations that are obtained both during the auditory and the tactile stimulation contexts. As a result, we can state that we are actually describing the neural bases of spontaneous blinks, i.e., those areas that are activated both during the spontaneous

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**Table 2**

Summary of the blink-related cortical activations, per monkey (M1/M2), per hemisphere (left/right)

<table>
<thead>
<tr>
<th>Area</th>
<th>M1/left hemisphere</th>
<th>M1/right hemisphere</th>
<th>M2/left hemisphere</th>
<th>M2/right hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual areas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1</td>
<td>[−9, −35, −5]</td>
<td>[4, −33, −5]</td>
<td>[−10, −25, −1]</td>
<td>[6, −21, 0]</td>
</tr>
<tr>
<td>V2v</td>
<td>[−6, −33, −6]</td>
<td>[4, −35, −2]</td>
<td>[−16, −27, −9]</td>
<td>[14, −29, −11]</td>
</tr>
<tr>
<td>V2d</td>
<td>[−8, −29, −6]</td>
<td>[6, −38, 5]</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>MST</td>
<td>[−11, −23, 1]</td>
<td>[12, −24, 5]</td>
<td>7.6</td>
<td>[−12, −24, 10]</td>
</tr>
<tr>
<td>Parietal area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPf</td>
<td>[−13, −19, 14]</td>
<td>[11, −17, 15]</td>
<td>[−14, −16, 13]</td>
<td>[12, −20, 13]</td>
</tr>
<tr>
<td>Medial areas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGen</td>
<td>[−5, −27, 2]</td>
<td>[4, −30, 2]</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>PCC</td>
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<td>[11, −17, 16]</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Area 24d</td>
<td>[2, −6, 17]</td>
<td>[1, −7, 16]</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Area 24c</td>
<td>[5, −1, 17]</td>
<td>[4, −2, 17]</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Somatosensory cortex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area 1/2</td>
<td>−</td>
<td>[−20, −10, 12]</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Area 2</td>
<td>[−5, −14, 11]</td>
<td>[17, −15, 13]</td>
<td>[−19, −10, 11]</td>
<td>[15, −10, 12]</td>
</tr>
<tr>
<td>SII/IV</td>
<td>[−19, −17, 14]</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Area 3a/3b</td>
<td>−</td>
<td>[−20, −6, 11]</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Insular and precentral cortex</td>
<td>−</td>
<td>[−15, −9, 14]</td>
<td>−</td>
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<td>PI</td>
<td>[−19, −2, −1]</td>
<td>[19, 3, −1]</td>
<td>6.4</td>
<td></td>
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<tr>
<td>ProM</td>
<td>[−22, 10, 0]</td>
<td>[22, 8, 0]</td>
<td>5.3</td>
<td>[22, 6, −1]</td>
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<tr>
<td>Temporal areas</td>
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</tr>
<tr>
<td>STS</td>
<td>5.6</td>
<td>[19, 2, −5]</td>
<td>4.2</td>
<td>−</td>
</tr>
<tr>
<td>A1/2</td>
<td>−</td>
<td>[−23, 10, 5]</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Area 11/13</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

For each area, peak location (x, y, and z coordinates with respect to the anterior commissure) and z-score at the local maximum are indicated. Bold characters code for the areas identified in 3 or more hemispheres. Italic characters code for the areas identified in 2 or less hemispheres. The areas are identified and labeled in reference to the nomenclature used in the Lewis and Van Essen atlas as available in Caret and in the Scalable brain atlas http://scalablebrainatlas.nclib.org. Abbreviations: STS, superior temporal sulcus area 2.
blinks generated during the auditory stimulation task and the spontaneous plus reflexive blinks generated during the tactile stimulation task.

This conjunction analysis also allows us to control for non-random blinking behavior induced by a specific experimental context (see Hupé et al. 2012 for a discussion on the consequences of fMRI methodology on blink studies). It is indeed unlikely that both sensory stimulation contexts used here induce, for example, shared attentional or decisional modulations, or shared eye movement strategies. Confirming this fact, none of the identified cortical blink-related areas can be associated with any of these potential confounds.

The only parameter that is shared between the 2 types of experimental contexts, apart from the fixation requirements is the random reward schedule. This reward event is much more frequent than the blink event, across all runs, including in monkey M1 in spite of its high blinking rate. As a result, reward-related signals contribute both to the signal of interest (blink-related) and to the remaining signal of noninterest. Confirming that this is the case and that our observations are not contaminated by cheek movement-related signals (Supplementary material, Potential confounds, cheek movements) or tactile stimulations to the face-related signals (Supplementary material, Potential confounds, tactile stimulations to the face) are also presented.

Neural Bases of Spontaneous eye Blinks

A Core Somatosensory Network

Spontaneous blink-related activations are obtained in a core somatosensory network composed of the upper face fields of 3 key somatosensory areas. Area 2 activations are reliably observed on the medial bank of the anterior most tip of the intraparietal sulcus. This location corresponds to a subsector of area 2 face field (Fig. 4A, Pons and Kaas 1986; Padberg et al. 2005), situated posterior to the perioral and intraoral area 2 subsector described by Schwarz and Fredrickson (1971) and Iwamura (2000), and medial to vestibular area 7t, which is located on the lateral bank of the anterior most tip of the intraparietal sulcus (Schwarz and Fredrickson 1971; Lewis and Van Essen 2000). Note that this area 2 face field is partially overlapping with the PF cytoarchitectonic region described by

Figure 4. Topographic somatosensory activations in areas 1, 2, 3a and 3b (A) and in the complex SII-PV (B). On the left are displayed statistical parametric maps (SPMs) showing the bilateral activations relative to the blink events in both monkeys (yellow scale, P < 0.001, uncorrected level). In the middle, the same activations are shown on a portion of the flattened map for the left hemisphere in both monkeys. The topographic organization for the corresponding regions is presented on the right part (A: adapted from Krubitzer et al. 2004; Padberg et al. 2005; Seeleke et al. 2012; B: adapted from Krubitzer et al. 1995). The gray areas correspond to the face representations. The solid lines correspond to the lips of the sulci, the dashed lines to the fundus of the sulci. The approximate locations of our blink-related activations (as presented in the middle part of the figure) on these topographic maps are represented in red. Abbreviations are given in Figure 3.
discussed above. However, self-generated tactile stimulations are known to induce weaker activations than tactile stimulations generated by another agent (Jiang et al. 1991; Chapman 1994). For example, tickling one-self is far less efficient than being tickled by someone else (Weiskrantz et al. 1971; Blakemore et al. 1998, 2000), because a feedforward efferent copy of the expected outcome of the action gates the sensory input within the somatosensory areas (Chapin and Woodward 1981; Blakemore et al. 1998). To our knowledge, previous fMRI studies on the neural substrates of spontaneous blinks did not highlight any specific activation in any of these early somatosensory processing areas (Hanakawa et al. 2008), to the exception of a single case study describing blink-related activations in the eye representation of the sensory cortex in a patient suffering from chronic corneal pain, both in the presence and absence of a noxious corneal stimulation (Moulton et al. 2012). As a result, the somatosensory activations we describe in our monkeys could be due to eye fatigue and corneal dryness induced by the fixation requirements they are submitted to. This would be in line with the cingulate and insular blink-related activations we describe below.

**A Larger Cortical Network**

Blink-related activations are also found in the medial bank of the intraparietal sulcus, in both hemispheres of both monkeys. These activations are located anteriorly to the medial intraparietal area MIP, cytoarchitectonically identified by Lewis and Van Essen (2000), possibly overlapping their medial ventral intraparietal area VIPm and their ventral area 5, 5v. It is clearly situated medially to the multisensory visuo-tactile and auditory-visuo-tactile site that we describe in the fundus of the intraparietal sulcus and which we attribute to the ventral intraparietal area VIP (Guipponi et al. 2013), and lies within the electrophysiologically defined area MIP (Colby and Duhamel 1991). Interestingly, this region coincides with a portion of the medial intraparietal sulcus in which low threshold microstimulations elicit nonvoluntary blinks in awake monkeys (Thier and Andersen 1998). We also describe another parietal blink-related activation on the medial wall, in a region corresponding to the posterior most portion of area PGm (nomenclature of Pandya and Seltzer 1982) or 7 m (nomenclature of Cavada and Goldman-Rakic 1989a). This region is considered as a higher-order supplementary somatosensory association area (Pandya and Barnes 1987) connected with area 3a/3b, area 2, SII/PV, and VIP (Leichnetz 2001). It has also been involved in oculomotor behavior (Thier and Andersen 1998), and indeed, it has recurrently been described as projecting to the FEF and supplementary eye field (SEF) oculomotor structures (Pandya and Barnes 1987; Cavada and Goldman-Rakic 1989b; Leichnetz 2001). Last but not least, it is recurrently identified in monkey fMRI studies describing the neural bases of saccadic behavior (precuneus in Kagan et al. 2010; Wilke et al. 2012) with a privileged functional connectivity with the FEF (Hutchison et al. 2012). All this taken together is compatible with the presence of a peri-orbital representation and a blink-related activation in this region as reported here. Overall we propose that the blink-related activations reported in these 2 posterior associative regions (MIP and PGm) reflect the sensory consequences of eyelid closure, similarly to what has been described in the somatosensory core regions, rather than their active motor correlate, as no specific blink-related activation can be described in key cortical oculomotor regions such as the FEF or the SEF.

**Figure 5.** Close-up of the occipital representations of the blink-related activations (boundaries in white solid lines) superimposed on retinotopic central (yellow scale, color transition being adjusted to t-scores = 4.8 FWE corrected level) and peripheral (blue scale) visual fields. Ce: central visual field; Pe: peripheral visual field. Other abbreviations as in Figure 3.

(Gregoriou et al. 2006) and characterized by oro-facial somatosensory responses (Roszi et al. 2008), though none of these studies mention a potential extension of this face region within the medial tip of the intraparietal sulcus, nor specific peri-orbital responses. *Areas 3a/3b* activations are situated on the anterior and posterior banks as well as in the fundus of the central sulcus, in the upper portion of its lower half extent, at a location described to represent the upper face (Fig. 4A, nose, cheeks, orbital region, including brows and forehead, Nelson et al. 1980; Krubitzer et al. 2004; Zhang and Britten 2004; Padberg et al. 2005; Wang et al. 2007; Seelke et al. 2012), consistent with the projection field of the ophthalmic branch of the trigeminal nerve (Nelson et al. 1980). The areas 3a/3b activations appear to spare the perioral and intraoral (Martin et al. 1999) as well as the arm-hand somatosensory representation, confirming the fact that our analysis is not confounded by potential variables of noninterest such as reward taking or uncontrolled for arm-movements (see Supplementary material, Localization of central sulcus activations, for an in depth description of the 3a/3b activation localization). Reliable activations are also observed in the somatosensory SII complex. The extent of this activation varied between the 2 monkeys and across hemispheres. In 3 hemispheres out of 4, 2 distinct activation peaks can be identified, possibly corresponding to SII and PV, respectively. As seen for the previous somatosensory areas, these activations are located within the face region of these somatosensory areas (Fig. 4B, Krubitzer et al. 1995).

Blinks, including spontaneous blinks, are expected to induce self-periorbital tactile stimulations, hence the observed tactile activation in the periorbital face region of different areas
A second medial blink-related region is also reliably identified in both hemispheres of both monkeys on the upper bank of the middle sector of the cingulate sulcus, matching the cytoarchitectonic definition of area 24d (Vogt et al. 2005) at a location compatible with the posterior cingulate face area (caudal portion of the M3 region, Morecraft et al. 1996, 2001) and the most caudal cingulate eye field (CEFc, Wang et al. 2004; Amiez and Petrides 2009) within the dorsal cingulate motor area CMAd (He et al. 1995; Picard and Strick 1996; Picard and Strick 2001). Early single cell recording studies (Olson et al. 1996) as well as more recent monkey fMRI studies describe oculomotor neuronal responses in this region (Ford et al. 2009; Kagan et al. 2010; Hutchison et al. 2012; Wilke et al. 2012). Corroborating this observation, this region is connected with the frontal eye fields (Huerta et al. 1987; Bates and Goldman-Rakic 1993; Morecraft et al. 1993). Retrograde transneuronal rabies virus tracing highlights strong polysynaptic projections from a region compatible with CEFc to the orbicularis oculi muscles responsible for eyelid closure (day 5, Gong et al. 2005). An additional medial activation is identified, in both hemispheres in monkey M1 and one hemisphere in monkey M2, anterior to CEFc, matching the cytoarchitectonic definition of area 24c (Vogt et al. 2005), and possibly corresponding to CEFr, within the rostral cingulate motor area CMAr (He et al. 1995; Picard and Strick 1996; Picard and Strick 2001). Indeed, microstimulations to CEFr evoke eye movements (Gentilucci et al. 1988; Godschalk et al. 1995) and this region, oligosynaptically connected to the extracortical motor neurons (Moschovakis et al. 2004) as well as to cortical oculomotor structures such as the FEF and SEF (Huerta et al. 1987; Bates and Goldman-Rakic 1993; Morecraft et al. 1993; Luppino et al. 2003), is activated during oculomotor behavior. A complementary analysis is presented in the Supplementary material (Potential confounds, Cheek movement confounds) confirming that these motor cingulate activations are not due to uncontrolled for cheek movements correlating with blink behavior. Still in monkey M1, in both hemispheres, a last cingulate region in the caudal most upper bank of the cingulate sulcus is possibly matching medial PE and area PE, cingulate part (PEci). Little direct anatomical and electrophysiological evidence is available regarding the contribution of this region to oculomotor behavior, though it appears to be activated by saccade execution in several monkey fMRI studies (Koyama et al. 2004; Baker et al. 2006) and microstimulations produce blinks (Thier and Andersen 1998).

Reliable blink-related activation can also be seen around the anterior pole of the lateral sulcus, in 2 distinct regions identified as the parainsular cortex Pi and the ProM praisocortical subdivision of the frontal opercular cortex PrCo. In addition, a bilateral ventral premotor 6Vb blink-related activation can also be seen in monkey M1. Interestingly, retrograde transneuronal rabies virus tracing highlight strong polysynaptic projection from both Pi and ProM to the orbicularis oculi muscles responsible for eyelid closure (day 5, Gong et al. 2005). Pi, ProM, and 6Vb are densely interconnected and reciprocally connected to the cingulate cortex, and specifically to CEFr (Barbas and Pandya 1987; Preuss and Goldman-Rakic 1989; Tokuno et al. 1997; Cippoloni and Pandya 1999; Morecraft et al. 2012). Complementing this indirect evidence for a contribution of these cortical regions in periorbital somatosensory processing, facial receptive fields have been described in Pi (Augustine 1996; Zhang et al. 1999) in particular during noiceptive stimulations (Zhang et al. 1999).

Cingulate and insular cortex activations are also reported in human blink studies (Bristow, Frith, et al. 2005; Hanakawa et al. 2008; Lerner et al. 2009; Hupé et al. 2012). The insula is highly interconnected with both the cingulate cortex, the frontal opercular cortex and the ventral most part of the pre-motor cortex, defining a limbic cortical network of sensory processing and integration (Barbas and Pandya 1987; Preuss and Goldman-Rakic 1989; Morecraft et al. 2007, 2012). In particular, the insula is considered as an integration center of visceral sensory and motor functions (Craig 2002), subserving the processing and the perception of internal stimuli and activating higher order representations of sympathetic homeostasis in response to stress (where homeostasis is the process by which an organism regulates itself to maintain its body in a stable peaceful state—no hunger, no thirst, no pain etc... Craig 2005). It is also proposed to be involved in the proproceptive awareness of blinks (Bristow, Frith, et al. 2005; Hupé et al. 2012) and indeed, the suppression of the urge to blink produces reliable insular and anterior cingulate functional activations in humans (Lerner et al. 2009). In this present study, the monkeys are required to maintain fixation over 85% of the total length of the runs, and blinks are processed so as not to interrupt the reward schedule and are thus not considered as fixation breaks. This fixation requirement is very demanding and puts a lot of stress on the eyes (all subjects of visual psychophysics experiments report on this). All this taken together indicates that these spontaneous blink-related activations can be viewed as cortical correlates of corneal dryness and possibly eye-related pain. These signals might be at the origin of an urge to blink, in an attempt to minimize the impact of the task requirements on the wellbeing of the subject. As a result, these insular and cingulate activations may be specific to the present study due to the demanding fixation requirements, unveiling cortical regions involved in the processing of eye and corneal strain/pain. It is however important to note that these fixation requirements, though specific, are not unusual to fMRI studies and might be at the origin of blink contamination in the results.

Overall, the somatosensory blink-related network and the larger cortical network described above allow us to identify an ensemble of cortical fields that are involved in the somatosensory, proprioceptive, and possibly nociceptive representations of the eyes. To our knowledge, this is the first time that such a network is reported, providing a precise whole-brain localization of these cortical eye fields and their potential intraindividual variability.

Striate and Extra-striate Cortical Areas

We report blink-related activations in V1, V2, and V3 as well as in medial superior temporal area MST which is known to process large field stimulations (Saito et al. 1986; Duffy and Wurtz 1991), but not in the medial temporal area MT which is described to favor local motion processing (Albright and Desimone 1987). Like in Hupé et al. (2012), these activations are mostly located in cortical regions coding the periphery of the visual field, as assessed by an independent retinotopic mapping allowing to distinguish between central and peripheral visual field representations (Fig. 4, see also Fize et al. 2003). Similar blink-related activations have been observed in human fMRI studies, both in the absence of any visual stimulation (Bristow, Frith, et al. 2005; Hupé et al. 2012) and in the presence of visual stimulations (Tse et al. 2010; Berman et al. 2012;
Hupé et al. (2012). When blinks are performed in total darkness, increased blink-related signals are observed in V1, V2, and V3 (Bristow, Frith, et al. 2005). In the presence of visual stimulations maintained unaffected during eye blinks (thanks to transpalatal visual stimulations), the hemodynamic response is higher during voluntary blinks than in the absence of blinks in visual area V3, indicating a blink suppression of the visual response, but remains almost constant in V2 and V1, suggesting an underestimation of blink suppressive mechanisms in the fMRI hemodynamic measures (Bristow, Frith, et al. 2005; Bristow, Haynes, et al. 2005). Indeed, single cell recording studies show that the firing rate of visual cortical neurons decreases during blinks (Buisserset and Maffei 1983; Gawne and Martin 2000, 2002). This blink-related neuronal modulation is more pronounced than what is observed following an external darkening of the visual scene (as is expected to be produced by blinks, Gawne and Martin 2000, 2002). This suppression of neuronal activity in the primary visual cortex is observed both following eye blinks and tactile stimulations around the eyes, indicating that it originates in the lid proprioceptive signal (Buisserset and Maffei 1983). This is interesting in 2 respects. First, in the present study as well as in Hupé et al. (2012), the neural correlates of this putative proprioceptive signal are observed in the absence of any activation of oculomotor prefrontal and parietal areas FEF and LIP (often observed during voluntary blinks, e.g., Bristow, Frith, et al. 2005; Bristow, Haynes, et al. 2005), indicating that blink suppression mechanisms might not be as similar to saccadic suppression mechanisms as initially thought (Volkmann 1986; Riddler and Tomlinson 1997), relying on the sensory proprioceptive consequences of blinks rather than on a central motor corollary discharge of blinks. Second, given the above discussion, the visual cortex activations most probably reflect both the visual consequences of blinks and the suppressive effect of an incoming proprioceptive signal. Recent observations demonstrate that the visual cortex receives hetero-modal projections from primary sensory cortices (auditory: Falchier et al. 2002; Rockland and Ojima 2003; somatosensory: Guipponi et al. submitted for publication). The present results suggest that it also receives direct projections from the primary somatosensory regions involved in proprioception, possibly from area 3a.

As noted by Hupé et al. (2012), it is however unclear why these blink-related activations are located in the peripheral visual field representation of the striate and extrastriate cortex, beyond 15–20° of eccentricity (see also Fize et al. (2003) for a precise mapping of visual eccentricity in the nonhuman brain occipital cortex). Several competing explanations are discussed in length by Hupé et al. (2012): (1) a stronger sensibility of the blood oxygen level-dependent (BOLD) signal to luminance transients in the periphery of the visual field, (2) the result of an intraocular scattering of light, (3) a differential adaptation or saturation of the BOLD signal in the center and the periphery of the visual field, (4) a differential central to peripheral gradient in the strength of blink suppression mechanisms and (5) postblink myosis. The present observations do not allow to favor one of these hypotheses against the others. A last possibility, unexplored by Hupé et al. (2012) and discussed in the previous paragraph, is that similar to what is observed for heteromodal auditory (Falchier et al. 2002; Rockland and Ojima 2003) and somatosensory (Guipponi et al. submitted for publication) projections onto the visual cortex, proprioceptive projections in this regions appear to preferentially target the peripheral visual field representation. Disambiguating these several potentially nonexclusive alternatives will require specific experimental designs.

**Functional Differences Between Spontaneous and Voluntary Blinks**

It is worth noting that several key oculomotor regions described in human voluntary blink production studies such as the FEF, the SEF and the LIP (Bodis-Wollner et al. 1999; Kato and Miyachi 2003b; Bristow, Frith, et al. 2005; Hanakawa et al. 2008; van Koningsbruggen et al. 2012) are not activated in the present study nor in human studies describing the neural correlates of spontaneous blinking (Yoon et al. 2005; Tse et al. 2010; Hupé et al. 2012). These regions, which are largely described as being at the origin of eye movement production and attentional control (Wardak et al. 2011; Wardak et al., 2012), are also thought to be at the origin of the blink-generation command (Bristow, Haynes, et al. 2005). In addition, the fronto-parietal network, including FEF and LIP, plays a key role in visuo-spatial attention (Corbetta and Shulman 2002; Ibos et al. 2013). This network is anticorrelated with the default-mode network (DMN, Vincent et al. 2007) and its level of activity is proposed to be dependent on the overall degree of attentional engagement of subjects in a given behavior (Anticevic et al. 2012; Wen et al. 2013). Corroborating this fact, Nakano et al. (2013) describe a blink-related activation in the DMN when subjects are viewing videos as compared with blank screens. This DMN activation correlates with a significant functional deactivation of the fronto-parietal network. The authors interpret this observation in terms of an attentional modulation of blink-related DMN activation by the cognitive context. Ramot et al. (2011) propose an alternative interpretation of these resting-state correlations. Indeed, they show that when subjects are at rest, eyes closed, their spontaneous hemodynamic fluctuations are coupled with eye movements, suggesting that part of the resting-state correlations might arise from “spontaneously emerging subconscious oculomotor behavior”.

**Relevance to Human fMRI Studies**

Importantly, our observations demonstrate that strong neural correlates of spontaneous blinks can be observed in the absence of cortical activations often taken as a signature of the involvement of blink-related mechanisms, namely, areas involved in the generation of voluntary blink oculomotor commands and areas contributing to blink-suppression mechanisms. As discussed in the previous paragraph, the prefrontal (SEF, FEF) and parietal (LIP) cortical blink-related oculomotor regions are identified in voluntary blink studies but not spontaneous blink studies, indicating that fMRI studies can still be contaminated by spontaneous blink-correlates in the absence of hemodynamic activations in these key areas. The cortical network underlying blink-suppression mechanisms (i.e., the process by which we are mostly unaware of the perceptual consequences of blinks) are difficult to identify due to the fact that blinks induce changes in the visual input to the retina. In a very elegant design in which retinal illumination was maintained constant thanks to a transpalatal visual stimulation, Bristow, Frith, et al. (2005) (see also Bristow and Haynes, et al. (2005)) demonstrate that, blink-suppression involves a cortical magnocellular pathway including area V5/MT and parietal and prefrontal regions presumably involved in perceptual awareness. None of these cortical areas are identified in the present study, indicating that the
absence of activation in these cortical regions involved in blink-suppression areas is not an unambiguous signature of the absence of blink contamination in the data. This has important implications on human fMRI studies (see also discussion in Hupé et al. 2012). Indeed, in a lot of protocols, the subjects’ eye behavior is not monitored inside the scanner. When eye position is monitored within the scanner, the obtained eye signal is included in the fMRI analysis model as a regressor of noninterest. As a result, the task-related activations described by the model are not confounded by uncontrollable eye-related cortical activations. However, to our knowledge, very few fMRI studies use blinks as a regressor of noninterest. This is due to at least 2 unspoken assumptions that: (1) there is no need to include blinks in the analysis if blink-related oculomotor or blink-suppression regions are not confounding the data—this assumption has been discussed above; (2) blink behavior is most often homogenous across the several conditions of a given fMRI design and blink behavior is mostly unaffected by the cognitive context. However, specific attentional or decisional processes have been shown to induce a nonrandom blinking behavior (e.g., Stern et al. 1984). Additionally, eye fatigue and fixation requirements may also differ from one experimental condition to the other within the same fMRI design. A simple way to counter these potential confounds would be to include blinks in the fMRI analysis model as a regressor of noninterest, though this may have as effect to alter the overall power of the main analysis. An alternative way would be to make sure that blink behavior is indeed homogenous throughout the different experimental conditions including at the end of the session when fatigue is expected to be maximal.

In conclusion, our observations show that spontaneous blinks induce somatosensory, proprioceptive, visual, and possibly nociceptive cortical activations without necessarily recruiting neither the prefrontal and parietal oculomotor centers nor the prefrontal, parietal, and medial temporal blink suppression centers. While this increases our understanding of the neural bases of spontaneous blinks, it also strongly implies that new criteria should be set to identify whether fMRI recordings are contaminated by a heterogeneous blink behavior or not.

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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References


