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Withdrawal of voluntary inhibition unravels the *off* state of the spontaneous blink generator

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ABSTRACT

Involuntary movements such as spontaneous eye blinks can be successfully inhibited at will. Little do we know how the voluntary motor circuits countermand spontaneous blinks. Do the voluntary inhibitory commands act to pause or to turn off the endogenous blink generator, or does inhibition intersect and counter the generator's excitatory outputs? In theory, the time taken for the system to generate an *after-inhibition blink* will reflect onto the form of inhibition. For instance, if voluntary commands were to turn the blink generator off then the *after-blink* latency would be fixed to the inhibition offset and reflect the time it takes for the generator to rebound and turn on. In this study we measured the *after-blink* latency from the offset of voluntary inhibition. Volunteers inhibited their blinks in response to sound tones of randomly varying durations. At the offset volunteers withdrew the inhibition and relaxed. Interestingly, the spontaneous *after-blinks* were fixed to the offset of the inhibition as if the generator rebounded from an off state. The *after-blink* latency was not related to the duration of the inhibition, and inhibiting even for a small fraction of the mean inter-blink interval generated an *after-blink* time-locked to the inhibition offset. Interestingly, the insertion of voluntary blinks after inhibition further altered the blink generator by delaying the spontaneous *after-blinks*. We propose that the inhibition of spontaneous blinks at the level of the generator allows for highly effective voluntary countermanding. Nevertheless, the withdrawal of such inhibition was strongly associated with motor excitation.

1. Introduction

In 2011, Fergal "Eyesore" Fleming won a staring contest by willfully inhibiting spontaneous eye blinks for 40 min and 59 s (Rawlinson, 2011). There is little data on the inhibition of spontaneous blinks that would allow us to compare Fergal's celebrated record with the rest of the population. Research has traditionally focused on the mechanisms for the generation of spontaneous blinks and the variations of the blinking behavior in health and diseases (Hall, 1945; Karson, 1983;Ponder and Kennedy (1927)). Interestingly, the blinking behavior, in particular the blink rate may contribute to the diagnosis of psychiatric illness such as depression and schizophrenia (Mackintosh, Kumar, & Kitamura, 1983). Still, few neuroscientific studies have focused on the aspects of the blinking behavior that make the voluntary inhibition of spontaneous blinking possible. Our anecdotal experiences suggest that we can successfully inhibit spontaneous blinking albeit for a limited period.

The established function of spontaneous blinking is to lubricate the eye (Doane, 1980). Blinks also "milk" the meibomian gland to increase lipid secretions and help form a stable tear film (Korb et al., 1994). However, only a small fraction of the spontaneous blink rate is sufficient to keep the eye lubricated (Doane, 1980; Karson, 1983). In addition to their protective role, blinks may influence higher brain functions such as by modulating the neuronal circuits involved in attention and introspection (Nakano, Kato, Morito, Itoi, & Kitazawa, 2013). Blinks may also serve a role in nonverbal communication. EEG measurements suggest that viewing another person blink results in significant neuronal activations (Nakano et al., 2013).

Spontaneous blinks occur without apparent sensory inputs and are very likely driven by an endogenous blink generator in the brain (Doughty, 2001; Kaminer, Powers, Horn, Hui, & Evinger, 2011). There are two main lines of evidence for a central generator. First, the blink rate is strongly associated with central dopamine activity. For instance, the administration of dopamine agonists in non-human primates increases the spontaneous blink rate (Karson, 1983). Furthermore,

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the depletion of dopamine such as in Parkinson's disease decreases the blink rate and treatments that elevate dopamine increase the blink rate (Biousse et al., 2004; Karson, 1983). Consistent with all this, the higher than normal blink rate in schizophrenic patients is reduced by neuroleptic medications (Mackert, Woyth, Flechtner, & Volz, 1990). Second, the blink rate is closely related to cognitive processing. For instance, in visuo-motor tasks the blink rate decreases with task difficulty (Drew, 1951). The rate is also modulated while reading texts, listening to sounds and watching movies, and entrained by rhythmic movements such as finger tapping (Cong, Sharikadze, Staude, Deubel, & Wolf, 2010; Doughty, 2001; Fukuda, 1994; Nakano et al., 2013; Nakano, Yamamoto, Kitajo, Takahashi, & Kitazawa, 2009). Nevertheless, sensory inputs from the eye also modulate the blink rate. Anesthesia of the cornea reduces the blink rate but it does not abolish blinking, whereas dry eyes or damage to the ocular surface increase the blink rate (Nakamori, Odawara, Nakajima, Mizutani, & Tsubota, 1997). Therefore the pace of the hypothetical central blink generator is determined by both intrinsic and peripheral factors.

The blink rate may be dramatically altered at will and brain imaging studies reveal a surprising number of cortical areas associated with this ability (Chung, Yoon, Song and Park (2006); Yoon, Chung, Song, & Park, 2005). In a PET study, the inhibition was associated with the insular cortex, primary and supplementary motor cortices (Lerner et al., 2009). The same areas were unveiled by using fMRI and a more detailed examination of the insular cortex suggested that this area is involved in encoding urge – which presumably builds up during the period of inhibition (Berman, Horovitz, Morel, & Hallett, 2012). The pre-frontal cortex is also associated with blink inhibition (Berman et al., 2012). Surprisingly, the primary visual cortex is also activated (in dark) and this is not resolved using corneal anesthesia (Tsubota, Kwong, Lee, Nakamura, & Cheng, 1999). In sum, a variety of brain structures associated with blink inhibition not only reflect the complexity of voluntary control of spontaneous blinking but also underline that movement inhibition may trigger a range of cortical consequences beyond motor inhibition such as the increase in the sense of urge. However, these findings provide little insights into how exactly the cortical motor outputs countermand the spontaneous blinks.

The empirical focus on spontaneous blinking and its voluntary inhibition has not been matched by theoretical efforts to address this involuntary–voluntary interaction. Based on the rhythmic nature of spontaneous blinks it is safe to assume that the blink generator can be depicted as an oscillator. Perhaps due to the complex mix of factors that can influence this oscillator the outputs are not entirely regular. Most published inter-blink interval (IBI) distributions are positively skewed, or "j-shaped" (Cruz, Garcia, Pinto, & Cechetti, 2011; Naase, Doughty, & Button, 2005; Ponder and Kennedy (1927)). The "j-shaped" irregularity of the generator's outputs could be described by a log-normal curve (Cruz et al., 2011) or using a stochastic statistical Ornstein–Uhlenbeck model (Hoshino, 1996). A separate study theoretically explored the inhibition of blinks by assuming a linear buildup of urge, but this linear model primarily aimed towards the analysis of fMRI data (Berman, et al., 2012). The aim of our study is to address the neuronal mechanisms involved in the voluntary control of spontaneous blinking by exploiting behavioral measurements from the period post-inhibition. Hypothetically, the voluntary inhibition of spontaneous blinks may be implemented by any one of four distinct strategies and reflect on the first spontaneous blink post-inhibition ("*after-blink*") (Fig. 1).

First, voluntary inhibition may involve a positive motor command to antagonize the (eyelid-closing) orbicularis oculi muscle. This mechanism is rather unlikely, as previous recordings from the inhibition period did not detect any blink-like activity in the orbicularis oculi muscle (our measurements from the inhibition period also confirm this) (Chung et al. (2006)). Still, if such a mechanism were to operate then it would leave the generator in an *on* state such that it would continue to generate excitatory outputs during the inhibition period. Essentially, the withdrawal

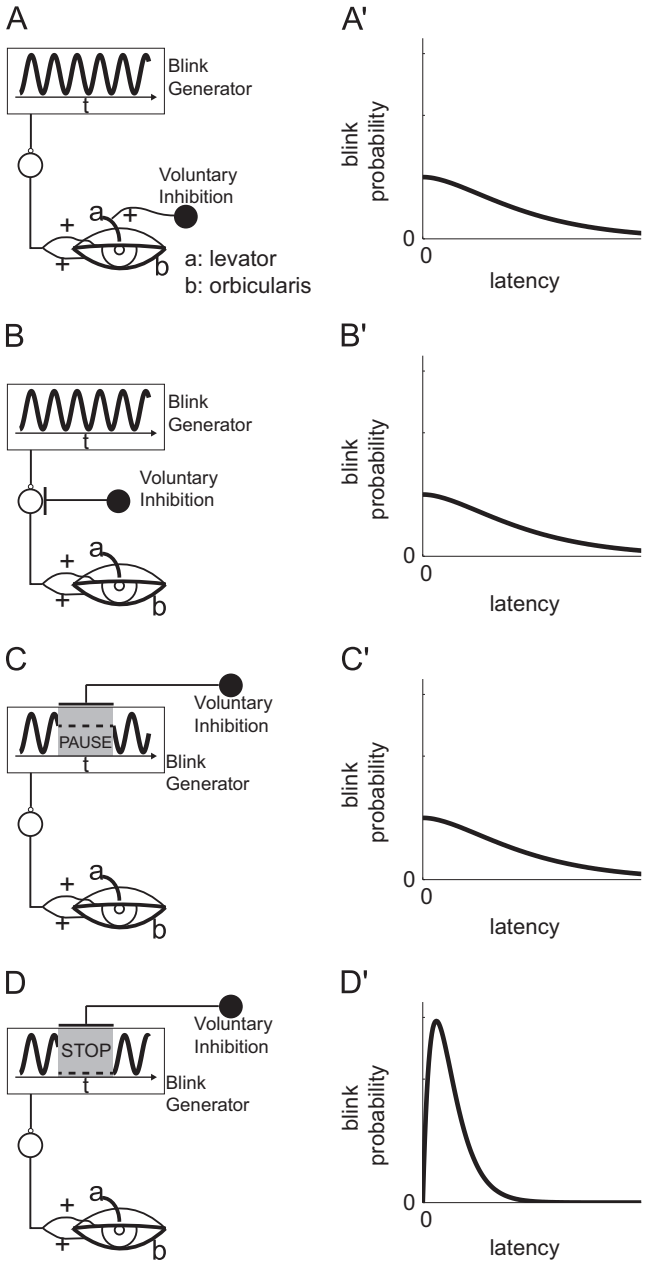

Fig. 1. Hypothetical strategies for voluntary inhibition of spontaneous blinks and associated predictions. (A) Peripheral inhibition, through strong excitation of the levator palpebrae superioris muscle antagonizing the closing of the eye by the orbicularis oculi, while the blink generator is kept in an *on* state, still emitting outputs. (A′) Upon the withdrawal of inhibition the outputs would continue to flow as during and before inhibition. Therefore, the withdrawal would have no systematic influence on the timing of the *after-blink*. Instead, the distribution of the *after-blinks* would be similar to their distribution after any random time point. (B) Action of voluntary inhibition via intersecting commands which null the generator's outputs after they are emitted. (B′) Similarly, the generator would be left in an *on* state, and the withdrawal of inhibition would have no effect on the *after-blink*. (C) Action of voluntary inhibition through a motor command which counter-balances the generator so as to achieve a *pause* state. (C′) Here the *after-blink* would be dictated by the random timing of the pre-inhibition blink relative to the onset of the pause state. (D) Voluntary inhibition targets and *stops* the blink generator, setting it to an *off* state. (D′) In this case only, the *after-blink* would be time-locked on the offset of inhibition and dictated only by the time taken by the generator to restart.