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Article in *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology* · November 2016

DOI: 10.1016/j.clinph.2016.10.089

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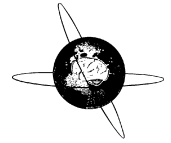
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Letter to the Editor

Rethinking blinking: No cognitive modulation of reflex eye protection in early onset blindness



The neurological consequences of blindness have been widely studied. One area that has escaped attention however, is the effect of blindness on defensive reflexes that subserves the protection of vision. The hand-blink reflex (HBR) provides an excellent method to address this topic because the modulation of its brainstem circuitry has been clearly characterised, and it can be easily interrogated with non-invasive methods. The HBR is elicited by electrical stimulation of the median nerve at the wrist, and consists in a rapid contraction of the orbicularis oculi muscles, with a clear defensive value for the eyes (Valls-Solé et al., 1997). The HBR is subserved by brainstem circuitry, which is finely modulated through a cortico-bulbar pathway when the hand to be stimulated is placed within the defensive peripersonal space surrounding the face (Bufacchi et al., 2016). This facilitation is under continuous cognitive control that reflects a sophisticated appraisal of the threat that is posed to the eyes, including both the probability of stimulus occurrence, and the presence of defensive objects protecting the eye (Sambo et al., 2012). Such modulation has a clear behavioural value: when a threat is closer, it poses a greater danger to the eyes, and a more effective blink reflex can mitigate the greater potential harm. Recording the HBR in blind individuals allowed us to address two important issues: (1) whether blind individuals also protect their eyes through the HBR response, and (2) whether, if present, their HBR displays the typical ‘far-near’ increase observed in sighted individuals.

Eight totally blind people (4 female, 26–57 years) volunteered. Two had early-onset blindness that developed prior to the age of 3 years, with no recollection of being able to see. The others had late-onset blindness, acquired after 3 years of age, and were able to recall visual experiences. Ten sighted people (9 female, 18–46 years) were used as controls.

Stimulation and recording procedures are detailed elsewhere (Sambo et al., 2012). Briefly, intense electrical stimuli were delivered transcutaneously to the median nerve at the wrist. Stimulus intensity was adjusted to elicit a clear HBR in three consecutive trials (blind group [mean \pm SD]: 13.1 ± 6.9 mA; controls: 17.5 ± 13.3 mA). Participants that did not show 3 consecutive HBR responses at the highest tolerable stimulus intensity, were considered non-responders (Sambo et al., 2012). Electromyographic activity (EMG) was recorded from the orbicularis oculi muscle bilaterally, using surface electrodes. Participants, seated with their forearms resting on a pillow in front of them, received 40 stimuli (inter-stimulus-interval \sim 30 s), delivered alternately with the hand either \sim 40–60 cm (‘far’; Fig. 1A) or \sim 4 cm (‘near’) from the eye. EMG was filtered (55–400 Hz), rectified, and aver-

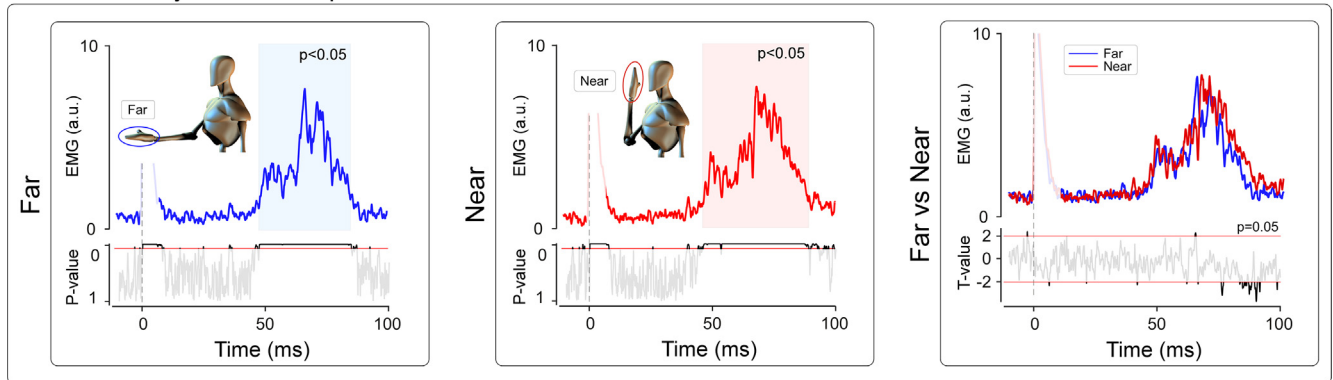
aged across eyes and trials, and HBR magnitude was expressed as area-under-the-curve (AUC) (Sambo et al., 2012). Far-near differences were reported as percentage of HBR magnitude in the ‘far’ position.

A clear HBR was present in five of the eight blind patients. This ratio is consistent with previous reports in healthy controls (Sambo et al., 2012). The early-onset blind participant showed a clear HBR, with normal onset (45 ms) and duration (48 ms). HBR responses were larger than baseline both in ‘far’ and ‘near’ hand positions (significant intervals: 47–85 and 46–89 ms, respectively; bootstrapping with respect to the pre-stimulus interval, Fig. 1A). Importantly, the HBR magnitude of the early-onset blind participant was virtually identical in ‘near’ and ‘far’ hand positions (AUC analysis: $p = 0.21$, paired *t*-test; point-by-point analysis: no difference; Fig. 1A). In contrast, in both late-onset blind participants and controls the HBR magnitude was larger in ‘near’ than in ‘far’ positions (blind group: $+49 \pm 9.3\%$; $p = 0.015$; controls: $+53\% \pm 11.7\%$; $p = 0.00024$, one-sample *t*-test; Fig. 1B). These percent increases were not different ($p = 0.45$, independent-sample *t*-test).

Therefore, we obtained two main results. First, blind individuals displayed a similar HBR to sighted individuals, regardless of the age at which their blindness developed. This finding indicates that the medullary HBR circuit is functional regardless of the age of blindness onset. Therefore, this circuit is likely to develop either during prenatal neurogenesis or in early infancy, and it remains functional throughout life. Second, individuals with late-onset blindness showed the robust ‘far-near’ effect commonly observed in sighted controls, whereas the individual with early-onset blindness did not (Fig. 1A). These results suggest that an effective cortical modulation of the HBR circuitry depends on having a functional visual system within a key and relatively small time interval during childhood, i.e. between 3 and 7 years of age. This modulation remains stable even when vision is subsequently totally lost.

A possible explanation is that early and late blind individuals use different reference frames when localising stimuli in external space. That is, early blinds do not automatically remap tactile information in external space, but instead use an anatomically anchored reference system (Crollen and Collignon, 2012). It follows that the HBR modulation relies on a brain function that integrates visuo-tactile spatial information and that this function does not fully develop until 3–7 years. The ventral intraparietal area (VIP) is a good candidate to subserves this function, given that VIP multimodal neurons represent the most likely substrate for integrating the spatial location of sensory stimuli belonging to different modalities, particularly in a face-centred reference frame (Graziano and Cooke, 2006). Furthermore, disruption of VIP function by TMS impairs the localisation of stimuli in external space only in late blind and sighted people (Crollen and Collignon, 2012).

Panel A: Early-onset blind patient



Panel B: Group comparisons

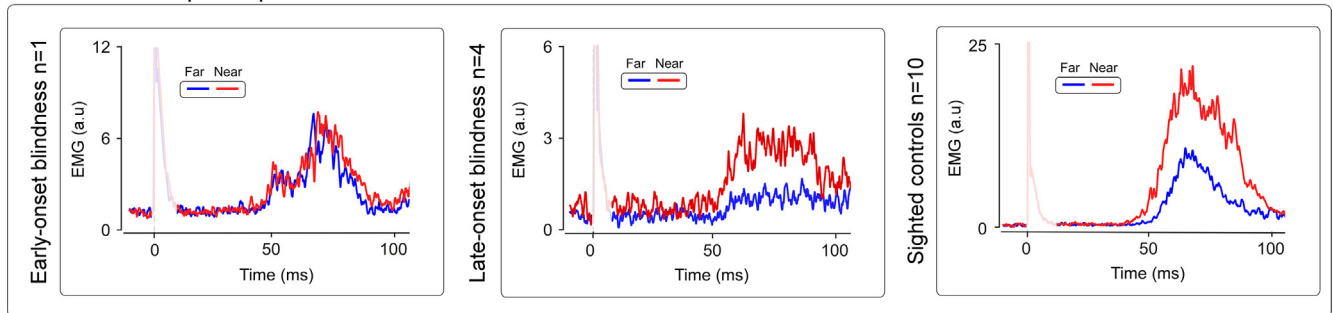


Fig. 1. HBR waveforms. *Panel A.* In the early-onset blind participant there was a clear HBR when the hand was in both ‘far’ (blue) and ‘near’ (red) positions (left and middle plots). However, their magnitude was not different (right plot). The top waveform of each plot expresses the EMG activity. The consistency of the HBR response is highlighted by the *p*-value waveforms at the bottom of the left and middle plots. The *t*-value waveform in the right plot shows the lack of difference between HBR magnitude in the two positions. *Panel B.* HBR responses recorded from the three groups of participants, while the hand was in ‘far’ (blue) and ‘near’ (red) positions. Contrary to the early-onset blind participant (left plot), both late-onset blind individuals (middle plot) and sighted controls (right plot) show a similar and clear enhancement of HBR magnitude when the hand was in the ‘near’ position (late-onset blindness participants: $+49 \pm 9.3\%$, $p = 0.015$; sighted controls: $+53\% \pm 11.7\%$, $p = 0.00024$; one-sample *t*-tests). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

A second, not mutually exclusive explanation is that in this key developmental period the importance of vision is learned, and the nervous system therefore deploys more resources to optimise the defence of the eyes. Consequently, the association between the stimulus being close to the eyes and the danger posed to the eye is made during this period, and the upregulation of the defensive reflex is developed.

Although these explanations require further interrogation, the observations reported here indicate that the nervous system develops the ability to purposefully modulate the magnitude of the defensive HBR if and only if vision is present during early childhood.

Acknowledgement

This study was supported by The Wellcome Trust [COLL JLAR-AXR], by the European Research Council (GDI), by an Australian Postgraduate Award from the Australian Government (SBW), by the EPSRC UK (RJB), and by the NHR Council of Australia (GLM).

Conflict of interest: None of the authors have potential conflicts of interest to be disclosed.

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Available online 3 November 2016