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Editorial

Brainstem avenues in Parkinson's disease research

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Reflex blinking is a relatively simple and stereotyped motor act. Despite this, a complex neuroanatomical framework, comprising brainstem circuitries as well as descending effects from subcortical and cortical areas, intervenes in the neural control of reflex eyelid movements (Cruccu et al., 2005; Valls-Sole, 2012; Bologna et al., 2013). Thus, investigations on reflex blinking represent a valuable tool in the field of clinical and experimental neurophysiology, in both healthy subjects and neurological conditions. For example, studies on the blink reflex in patients with Parkinson's disease and other parkinsonian syndromes have provided evidence in these conditions of the pathophysiological involvement of the brainstem, resulting from either neurodegenerative changes or indirect basal ganglia effects on blink reflex circuits due to altered central dopaminergic activity (Agostino et al., 1987; Valls-Solé, 2000; Bologna et al., 2013, 2017).

As neurophysiologists, we are all are grateful to Dr. Kimura for his seminal works on the blink reflex, elicited by stimulating the supraorbital branch of the trigeminal nerve, and for pioneering the development of this technique into a routine procedure in neurological practice (Kimura et al., 1969, 1970, 1975). Since then, the trigeminal blink reflex has been further investigated in healthy humans and in various neurological conditions with the help of innovative experimental approaches. Among these, some investigations have expanded our knowledge of the multiple afferent routes in brainstem blink circuits that mediate the blink reflex. Studies performed in the 1980s showed that electrical stimulation of the corneal receptors, which activates Aδ and C free nerve endings, also elicits a reflex from the orbicularis oculi muscle (corneal reflex) (Accornero et al., 1980; Agostino et al., 1987). The observation that the corneal reflex is less prone to habituation phenomena resulting from low frequency repetitive stimulation than the blink reflex indicates that the two reflex movements are mediated through different neural substrates (Berardelli et al., 1985). Studies on the corneal reflex represent one of the earliest experimental demonstrations that distinct, albeit partially overlapping brainstem circuits, might be involved in generating the orbicularis oculi muscle reflex response through the activation of distinct afferent routes (Accornero et al., 1980; Berardelli et al., 1985). It has also been demonstrated that the orbicularis oculi reflex can be triggered by stimulating the peripheral nerve of the upper and lower limbs through the activation of non-nociceptive Aβ afferents, which in turn project to mechano-sensitive brainstem interneurons in the medullary reticular area. The relaying afferent inputs then ascend from the medulla to the efferent branch of the reflex circuit, i.e. the facial motor neurons that innervate the orbicularis oculi muscle (Valls-Solé et al., 1994). Lastly, studies have also demonstrated that reflex blinking may be induced by stimulation modalities other than those targeting the somatosensory system, including light stimulation (Yates and Brown, 1981) and acoustic stimuli (Brown et al., 1991).

In this issue of *Clinical Neurophysiology*, Weise et al. present a method of eliciting a blink reflex that involves sensory afferents conducted by the auricular branch of the vagus nerve, via the superior jugular ganglion to the spinal trigeminal nucleus and through the reticular formation (Weise et al., 2019). The afferent signals then overlap the trigeminal nerve afferents from the supraorbital nerve transmitted polysynaptically through the pontomedullary reticular formation. The technique proposed by Weise et al. applies percutaneous monophasic electric stimuli, each lasting 100 μs, with an interstimulus interval of 20 ± 10 s (to avoid habituation phenomena), delivered at an intensity 8 times greater than the perceptual threshold. The technique differs from the traditional methods of the blink reflex elicited by trigeminal or median nerve stimulation by placing the stimulating skin electrodes on the inner side of the tragus (at the outer ventral edge of the external auditory meatus) while electromyographic activity is recorded from both orbicularis oculi muscles using surface electrodes. In this study, the authors also thoroughly tested the blink reflex circuits evoked by trigeminal and median nerve stimulation. The data collected from patients with Parkinson's disease were compared with those from healthy controls. No differences were detected between patients and controls in the latencies and amplitudes in any of the three types of blink reflexes examined, which indicates that no abnormalities affect the brainstem circuits in Parkinson's disease. Moreover, the results in the Parkinson's disease group cannot be ascribed to cognitive abnormalities or to the presence of REM sleep behaviour disorders. These findings thus go against the general belief that brainstem degeneration in Parkinson's disease involves the vagal nuclei complex, even from the early stages of the disease, and that this degeneration results in non-motor signs in this condition (Braak et al., 2003). The authors acknowledge the potential limitations of the study, which include the lack of a detailed assessment of non-motor symptoms in the patients sample and the possibility that the results were in part be due to the pharmacological therapy being taken by the patients. The results may also have been affected by the heterogeneity of the patient

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sample, which is a common limitation in neurophysiological research, particularly in studies based on relatively small sample sizes. Furthermore, it was not possible to draw any conclusions on the possible relationship with other non-motor symptoms, such as constipation or cardiac dysfunction, because they were not tested.

Although the results of the present study are negative, the authors should receive credit for their innovative approach. Indeed, this study has demonstrated that the blink reflex may be evoked by electrical stimulation of the vagus nerve. This is an important step forward since abnormalities of the vagus nerve are currently assessed exclusively by indirectly measuring heart rate variability (Shibata et al., 2009) or by means of ultrasound (Pelz et al., 2018). Further investigations in healthy subjects are needed to gain a better understanding of the physiological properties of the brainstem circuits related to vagus nerve stimulation, i.e. habituation, sensitization and pre-pulse inhibition, as has previously done for the trigeminal blink reflex circuit (Sanes and Ison, 1983; Valls-Solé et al., 1994). Moreover, it would be useful to investigate, whenever possible, the recovery cycle of the blink reflex elicited by vagus nerve stimulation (as done for the trigeminal blink reflexes) to understand whether it is also affected by descending basal ganglia projections, as demonstrated in animal models of parkinsonism and in patients with Parkinson's disease. The results the present study also raise the possibility of using this technique to investigate neurodegenerative phenomena of the vagus nerve complex in atypical parkinsonian disorders characterized by marked brainstem degeneration, such as progressive supranuclear palsy (Valls-Solé, 2000; Bologna et al., 2009, 2017). The various techniques currently available to assess reflex blinking are based on circuits with a varying sensitivity to different patterns of brainstem pathology, such as those found in Parkinson's disease and atypical parkinsonian disorders. It is possible that the neurophysiological approach proposed by Weise et al. may provide an effective means of discriminating between these different parkinsonian syndrome patterns.

In conclusion, the study by Weise et al. indicates that the neurophysiological assessment of the blink reflex circuits is not becoming obsolete but can, on the contrary, still be considered a valuable experimental approach. The combination of various neurophysiological techniques and experimental methods, which may even include neuroimaging (Bologna et al., 2016), are likely to provide a better characterization of reflex blinking and shed light on its neural control systems. Blink reflex testing based on various brainstem avenues can thus play an important role, for both pathophysiological and clinical purposes, not only in patients with Parkinson's disease, particularly in selected subtypes, but also in patients with atypical parkinsonian disorders.

Conflict of interest

None of the authors have any potential conflicts of interest to disclose.

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