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REVIEW ARTICLE

The cerebellum and the acoustic startle response: Can non-invasive brain stimulation provide new insights?

Dominika Besterciová [1], Rastislav Rovný [1], Igor Riečanský [1,2,3]

[1] Department of Behavioural Neuroscience, Institute of Normal and Pathological Physiology, Centre of Experimental Medicine, Slovak Academy of Sciences, Bratislava, Slovakia. [2] Social, Cognitive and Affective Neuroscience Unit, Department of Basic Psychological Research and Research Methods, Faculty of Psychology, University of Vienna, Austria, [3] Department of Psychiatry, Faculty of Medicine, Slovak Medical University, Bratislava, Slovakia.

Correspondence to: MUDr. Igor Riečanský, PhD., Department of Behavioural Neuroscience, Institute of Normal and Pathological Physiology, Centre of Experimental Medicine, Slovak Academy of Sciences, Sienkiewiczova 1, 813 71 Bratislava, Slovakia
e-mail: igor.riecansky@savba.sk

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Abstract

Modern techniques of non-invasive brain stimulation have opened new possibilities to study human brain functions. They represent a new approach to tackle information processing within the brain and brain structures, including the cerebellum. There is a lot of evidence that the function of the cerebellum is not restricted to the control of movements, but the understanding of its role in behavior is still unsatisfactory. It has been recognized that the cerebellum contributes to many non-motor functions including attention, working memory, language, and emotions. Here we consider the role of the cerebellum in the acoustic startle response, a reflexive protective reaction to a sudden loud sound. Acoustic startle response has an important role in translational research since it is present across species and can be easily assessed and experimentally modified. It is well suited for studying auditory information processing and sensorimotor gating. Some forms of acoustic startle response modulation, such as prepulse inhibition, are considered as endophenotypes of neuropsychiatric disorders. In this review, we describe the current knowledge on the involvement of the cerebellum in the acoustic startle response and suggest future research directions utilizing neurostimulation which could increase the understanding of the role of the cerebellum in behavior.

Abbreviations:
acoustic startle response (ASR), blood oxygenation level-dependent signal (BOLD signal), electroencephalography (EEG), electromyography (EMG), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), nucleus reticularis pontis caudalis (nRPC), positron emission tomography (PET), prepulse facilitation (PPF), prepulse inhibition (PPI), transcranial alternating current stimulation (tACS), transcranial electrical stimulation (tES), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), non-invasive brain stimulation (NIBS).

Methodological challenges of studying cerebellar functions in humans

The cerebellum is no longer viewed solely as the coordinator of motor functions (Klein *et al.* 2016). In the second half of the previous century, the observations of non-motor symptoms accompanying cerebellar damage have led to the description of a new clinical

entity: the cerebellar cognitive affective syndrome. Patients with this syndrome display a wide spectrum of impairments, including deficits in executive functions and working memory, language, spatial cognition, as well as mood and personality changes (Hoche *et al.* 2018; Schmahmann & Sherman, 1998). Because of that, the theories of the function of the cerebellum have started to reflect the previously ignored non-motor processing within both cognitive and affective domains.

Studying cerebellar functions in humans is methodologically challenging. Probably the most widely used approach in the last years has been functional neuroimaging using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), which has revealed many interesting facts about cerebellar engagement in non-motor tasks. However, the blood oxygenation level-dependent signal (BOLD) detected by fMRI may be difficult to interpret due to excessive folding of the cerebellum (Diedrichsen *et al.* 2009, 2019) and it remains unclear whether the BOLD signal reflects the activity of Purkinje cells (the output cells of the cerebellar cortex) or cerebellar cortical interneurons. Interestingly, it has been reported that interneurons, especially granular cells, contribute most to the energy consumption of the cerebellum (Howarth *et al.* 2012) and their activity has a significant impact on cerebellar blood flow (Mathiesen *et al.* 1998). Electrophysiological methods, electroencephalography (EEG) and magnetoencephalography (MEG), also face the problem of the complicated cerebellar cytoarchitecture and folding, and specific approaches need to be employed to reliably detect neural signals from the cerebellum using these methods (Andersen *et al.* 2020).

Recently, considerable progress in the research of the cerebellum in humans has been achieved by the use of non-invasive brain stimulation (NIBS) methods – transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). In TMS, an electromagnetic coil is used to create a magnetic field which induces electric currents in the targeted tissue interfering with neuronal activity (Barker *et al.* 1985). In tES, a weak direct current (transcranial direct current stimulation – tDCS) or alternating current (transcranial alternating current stimulation – tACS) flows between stimulating electrodes (anode and cathode), affecting neural tissue (Antal *et al.* 2008; Nitsche & Paulus, 2000). NIBS techniques are safe, easy to administrate, and result in both short- and long-term effects on brain activity and behavior. Short-term effects are due to modulation of resting membrane potential leading to increased or decreased probability of neuronal excitation (Nitsche & Paulus, 2000) while long-term effects are mediated by the processes of synaptic plasticity (Kronberg *et al.* 2017; Podda *et al.* 2016; Rahman *et al.* 2017).

The first neurostimulation studies of the cerebellum employed TMS to modulate an inhibitory tone which the cerebellum exerts over the primary motor cortex (so called cerebellar brain inhibition) (Pinto & Chen, 2001; Ugawa *et al.* 1995). Subsequent studies have shown that cerebellar TMS can be used to modulate non-motor processes as well (Arasanz *et al.* 2012; Argyropoulos, 2011; Desmond *et al.* 2005; Ferrari *et al.* 2021; Schutter & van Honk, 2006). Following the reports of efficacy of cerebellar TMS, the protocols of cerebellar tDCS have been introduced (for a review, see Ferrucci *et al.* 2015). Furthermore, tACS has also been shown to affect cerebellar activity, even though so far only motor processes have been investigated by this method (Giustiniani *et al.* 2021; Naro *et al.* 2017; Spampinato *et al.* 2021; Wessel *et al.* 2020). Overall, the research shows that NIBS opens new possibilities for studying cerebellar processing in humans, enabling researchers to revisit the concepts of cerebellar function.

Acoustic startle response

Acoustic startle response (ASR) is a reflexive protective motor response to a sudden intense and potentially dangerous acoustic stimulus. The startle response involves quick contractions of muscles, eyeblink and increased heart rate. The eyeblink component of the startle response associated with *musculus orbicularis oculi* contraction is most commonly assessed to quantify ASR in humans and is usually measured with non-invasive surface electromyography (Blumenthal *et al.* 2005).

The primary neuronal pathway of ASR consists of three to five synapses. The startle stimulus first activates receptors in *cochlea* and neurons of the cochlear nucleus. The signal is then transmitted via auditory afferent projections to the reticular formation, specifically to *nucleus reticularis pontis caudalis* (nRPC). From nRPC the information is sent via facial nerve to *musculus orbicularis oculi*, resulting in startle-induced contraction and eyeblink (Lee *et al.* 1996). Importantly, activity of nRPC is modulated by various brain areas, including cortical regions, amygdala, cerebellum and basal ganglia (Shammah-Lagnado *et al.* 1987; Hormigo *et al.* 2018), activity of which can thus modulate ASR.

Since ASR is present across species, it provides a valuable tool for translational research. The measurement of basic startle reactivity has been utilized in many developmental (Ebishima *et al.* 2019; Rybalko *et al.* 2015), pharmacological (Geyer *et al.* 2001), genetic (Karl *et al.* 2010; Plappert & Pilz, 2001; Shoji & Miyakawa, 2018) and clinical studies (Kumari *et al.* 2001; Larsen *et al.* 2002; Morgan *et al.* 1996). Increased ASR has been linked with several disorders, including posttraumatic stress disorder (Morgan *et al.* 1996), obsessive-compulsive disorder (Kumari *et al.* 2001) or panic disorder (Larsen *et al.* 2002). It has been reported that the magnitude of ASR is positively associated with state anxiety (Poli & Angrilli, 2015). The factors affecting ASR include age (Ludewig *et al.* 2003) and gender (Bianchin a Angrilli, 2012), but see Ludewig *et*

al. 2003; Armbruster *et al.* 2014). In women, ASR varies across menstrual cycle and is higher during ovulation and later luteal phase compared to the other phases of the cycle (Epperson *et al.* 2007; Armbruster *et al.* 2014). Startle reactivity is also positively associated with personality traits such as trait anxiety (De Pascalis *et al.* 2013) and aggressivity (Heesink *et al.* 2017) and negatively associated with psychopathic personality (Oskarsson *et al.* 2021). However, it is important to note that compared to basic startle reactivity more extensive research has focused on various forms of ASR modulation such as affective modulation (e.g. fear-potentiation), habituation, or prepulse inhibition (PPI) and prepulse facilitation (PPF) (i.e. reduction/enhancement of ASR by stimuli of lower intensity when presented prior to startling sounds).

The role of the cerebellum in ASR

Hypotheses of the involvement of the cerebellum in ASR have been postulated on a foundation of the following findings: 1) the presence of anatomical connectivity between the cerebellum and nRPC, 2) alterations in ASR magnitude and its modulation in gene-knockout mice with cerebellar deficits, 3) association between cerebellar activation and ASR in functional neuroimaging studies in humans.

Studies in rodents and primates confirmed the existence of the anatomical connection from the cerebellum to nRPC. More specifically, these studies used autoradiography and retrograde tracing to demonstrate that neurons in the cerebellar nuclei, predominantly *nucleus fastigii*, project to the nRPC (Batton *et al.* 1977; Shammah-Lagnado *et al.* 1987). Thus, it seems reasonable to expect the existence of this projection also in humans, via which the cerebellum may exert influence on ASR and other processes regulated by nRPC.

Several studies investigated the involvement of the cerebellum in ASR using genetically modified mouse lines. For example, Park *et al.* (2002) demonstrated that mice carrying the cerebellar deficient folia *(cdf)* mutation, causing abnormal development and structural alterations of the cerebellum, exhibit greater startle reactivity but weaker PPI and fear-potentiated startle compared to wild-type control mice. Moreover, transgenic mice lacking nuclear receptor TAK1 gene, which is essential for cerebellar development, show reduced startle reactivity, habituation, and PPI (Kim *et al.* 2010). Thus, genes implicated in cerebellar development and function seem to play a role in ASR.

Support for the role of the cerebellum in the startle reflex has come also from human research. A combined fMRI-EEG measurements in healthy young men have revealed increased cerebellar activation after the presentation of an air puff startle stimulus (Neuner *et al.* 2010). On the other hand, in a study by Pissiota *et al.* (2002) startle stimulation activated medial pons region, corresponding to the location of the nRPC, while activity of the cerebellum correlated with acoustic startle amplitude during startle repetition, indicating its role in habituation of ASR (Pissiota *et al.* 2002).

How can cerebellar NIBS advance the knowledge of the startle reflex?

The startle reflex has long been recognized as an important behavioral test system commonly used to study the physiology and pathophysiology of cortical and subcortical neural circuits. Abnormalities of the startle reflex and its modulation have been observed in multiple neuropsychiatric disorders (Kumari *et al.* 2001; Larsen *et al.* 2002; Morgan *et al.* 1996). Subcortical brain regions implicated in the pathogenesis of these disorders are not an easy target for therapeutic interventions. NIBS has proved to be an effective way to modulate the activity of the cerebellum (Ferrucci *et al.* 2015). However, the neurophysiology of the startle reflex has not yet been examined using cerebellar neurostimulation, as far as we are informed. Although it is not known whether cerebellar NIBS effectively modulates basic startle reactivity, neurostimulation studies of the cerebellum highlight the potential of this approach for the studies of ASR. For instance, Bocci *et al.* (2018) demonstrated that cerebellar tDCS affects the hand-blink reflex, an eyeblink elicited by electrical stimulation of the median nerve, suggesting that the cerebellum is implicated in defensive behaviors (Bocci *et al.* 2018). Furthermore, cerebellar TMS and tDCS were used in several studies to target various aspects of associative learning assessed using eyeblink conditioning paradigms (Hoffland *et al.* 2012; Mitroi *et al.* 2020; Monaco *et al.* 2014; Monaco *et al.* 2018; Zuchowski *et al.* 2014). The advent of novel NIBS techniques greatly extends the possibilities to study cerebellar functions. Advancing knowledge about the cerebellar involvement in the startle reflex may help to identify novel treatment targets in neuropsychiatric disorders. It may be thus useful to follow up the findings summarized in this brief review and investigate the role of the cerebellum in the startle reflex using NIBS.

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