



Non-invasive stimulation of the motor cerebellum has potential cognitive confounds



The cerebellum has been known to play an important role in motor control for over a century. Seminal work by Holmes highlighted that damage to the cerebellum severely impairs motor coordination [1]. Converging evidence from behavioural, neurophysiological, neuropsychological, and neuroimaging studies has since highlighted the functional role of cerebellar-motor interactions in motor behaviours. Specifically, cerebellar lobules IV–VI and VIIIB–VIII (which we will refer to as the “motor cerebellum”) have reciprocal anatomical connections with cortical motor areas [2]. Somatotopically organised primary and secondary motor representations that functionally interact with the primary motor cortex have been described in cerebellar lobules V and VIII respectively [3]. These cerebellar-motor networks have been established as playing a critical role in motor control.

The cerebellum also plays a well-documented role in higher-order functions [2,4,5]. In primates, cerebellar Crus I and Crus II are reciprocally connected to prefrontal cognitive areas [2,3,5,6]. Clinically, cerebellar lesions or atrophy can lead to “Cerebellar Cognitive Affective Syndrome”, which is characterized by problems in executive function, affect, and language [4]. Functional neuroimaging and non-invasive brain stimulation studies in healthy populations similarly demonstrate a cerebellar role in cognition and language [7,8] with Crus I and II specifically involved in these higher-order functions [6]. This has led to a general consensus that prefrontal-projecting Crus I and II (which we will operationally define as the “cognitive cerebellum”) contribute to higher-order functions such as cognition and language [5].

Critically, the division of motor and cognitive function within the cerebellum is often overlooked in studies using transcranial stimulation. A large body of work has aimed to modulate cerebellar function through non-invasive brain stimulation [9], and the majority of this research aims to affect motor function. However, it is difficult to stimulate motor regions of the cerebellum without also stimulating the overlying cognitive cerebellum (Fig. 1; see also [10]). Cerebellar Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current stimulation (tDCS) targeting motor functions typically place the coil or stimulating electrode 3cm lateral to the inion, or 3cm lateral and 1cm inferior to the inion. However, from these positions, any stimulation reaching the deep lying motor cerebellum would first have to pass through the cognitive cerebellum. We therefore argue that it is important to carefully consider potential cognitive confounds in cerebellar stimulation studies aiming to affect motor circuitry.

Findings from non-invasive stimulation studies are consistent with our proposal that successfully affecting the function of the pathway between the cerebellum and primary motor cortex

requires the stimulation of deeper lying regions. Studies using TMS to induce cerebellar-brain inhibition (a measurement of cerebellar motor projections) have found that this effect is only reliably induced using specialized coils that produce stimulation with a deeper focal point, and only at relatively high intensities of stimulation compared to more superficial cortical targets [10]. Similarly, tDCS studies have shown that effective modulation of cerebellar motor circuits can only be achieved using relatively high intensities of stimulation (2ma) compared to those that can modulate cerebral motor areas (1ma; [11]). Notably, increasing stimulation intensity leads not only to an increase in distance, but also an increase in the spread of the stimulation. This lack of focality, coupled with the aforementioned application at a site that is closer to the cognitive cerebellum, makes it highly likely that transcranial stimulation targeting the motor cerebellum also stimulates the cognitive cerebellum.

The high likelihood that cerebellar transcranial stimulation affects cognitive networks has important implications for the interpretation of cerebellar transcranial stimulation studies. For example, prior work has shown that cerebellar stimulation can modulate the rate of motor adaptation in both reaching and walking tasks [12–14]. However, in these studies, cerebellar stimulation appears to have no effect on the initial motor after-effects that are a hallmark of internal model recalibration - considered the primary contribution of the motor cerebellum. It is notable that analogous increases in the learning rate with no change in motor after-effects also occur when participants perform motor adaptation tasks with an explicit strategy [15]. Rather than affecting motor adaptation solely via a cerebellar-motor circuit, a plausible alternative suggestion is that the effect of cerebellar stimulation may result from modulation of the cerebellar-cognitive network (i.e. through modifying explicit mechanisms such as the use of strategies [16]), or an interplay between both circuits (see also [17]). This could potentially explain the difficulties seen in studies attempting to separately modulate the implicit and explicit components of motor adaptation [18], and could plausibly explain the results of work reporting effects of cerebellar stimulation on motor savings [13], as recent research suggests savings may be linked to explicit learning mechanisms [19].

In summary, it is unlikely that presently available transcranial stimulation techniques can stimulate the motor cerebellum without also affecting the cognitive cerebellum. This has important implications for the design and interpretation of cerebellar transcranial stimulation studies aiming to modulate motor functions. Such studies should consider potential effects of prefrontal-

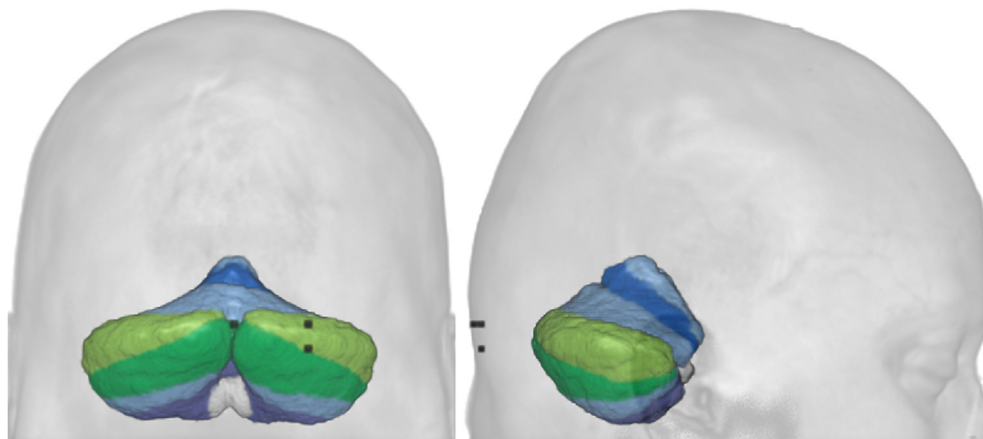


Fig. 1. Posterior and right lateral renders of the cerebellum identified by the SUIT atlas [20]. Green areas present regions involved in prefrontal-projecting cerebellar networks (Light and dark green present Crus I and Crus II, respectively) while blue regions indicate areas involved in motor-projecting cerebellar networks (lobules V and VIII, which contain the primary and secondary hand representations within the cerebellum, are presented in dark blue and purple, respectively, while other regions implicated in motor function are shown in light blue). Black markers indicate the inion (central) and two frequently used sites for cerebellar stimulation (3cm lateral to the inion, or 3cm lateral and 1cm inferior to the inion). Note that when using these locations, transcranial stimulation is effectively directed at cognitive cerebellar regions rather than in motor cerebellar regions. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

projecting cerebellar networks that are involved in cognition and language.

Declaration of competing interest

None of the authors have any conflicts of interest to declare.

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