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Neurorestorative effects of cerebellar transcranial direct current stimulation on social prediction of adolescents and young adults with congenital cerebellar malformations

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A R T I C L E I N F O

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Action prediction

A B S T R A C T

Background: Converging evidence points to impairments of the predictive function exerted by the cerebellum as one of the causes of the social cognition deficits observed in patients with cerebellar disorders.
Objective: We tested the neurorestorative effects of cerebellar transcranial direct current stimulation (ctDCS) on the use of contextual expectations to interpret actions occurring in ambiguous sensory sceneries in a sample of adolescents and young adults with congenital, non-progressive cerebellar malformation (CM).
Methods: We administered an action prediction task in which, in an implicit-learning phase, the probability of co-occurrence between actions and contextual elements was manipulated to form either strongly or moderately informative expectations. Subsequently, in a testing phase, we probed the use of these contextual expectations for predicting ambiguous (i.e., temporally occluded) actions. In a sham-controlled, within-subject design, participants received anodic or sham ctDCS during the task.
Results: Anodic ctDCS, compared to sham, improved patients' ability to use contextual expectations to predict the unfolding of actions embedded in moderately, but not strongly, informative contexts.
Conclusions: These findings corroborate the role of the cerebellum in using previously learned contextual associations to predict social events and document the efficacy of ctDCS to boost social prediction in patients with congenital cerebellar malformation. The study encourages the further exploration of ctDCS as a neurorestorative tool for the neurorehabilitation of social cognition abilities in neurological, neuropsychiatric, and neurodevelopmental disorders featured by macro- or micro-structural alterations of the cerebellum.

1. Introduction

It is acknowledged that cerebellar disorders, beside difficulties in motor coordination, also comprise deficits in the socio-affective domain. Since the description of the Cerebellar Cognitive Affective Syndrome (CCAS; Schmahmann & Sherman, 1998), encompassing difficulties in executive functions, language, spatial cognition, affect and behavior regulation, the role played by the cerebellum in broader than motor only functions has become clear. In this perspective, the literature has flourished with an increasing number of studies on the contribution of the cerebellum in social cognition (Pierce & Péron, 2020; Sokolov, 2018; Van Overwalle et al., 2020).

Social symptoms in patients with cerebellar disorders might reflect deficits in distinct internal simulative mechanisms, dealing with low-level processing of the perceptual features of observed movements, or with high-level mental inferences (Coricelli, 2005). This is suggested by the difficulties in this patients in movement perception (Abdelgabar et al., 2019; Cattaneo et al., 2012), emotion processing (Thomasson

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et al., 2019) and regulation (Houston et al., 2022), and mentalizing abilities (Clausi et al., 2019; Sokolovsky et al., 2010). Such deficits may result from an acquired lesion of the cerebellum, as described in the initial report of the CCAS (Schmahmann & Sherman, 1998), and from genetic and environmental risk factors (D'Arrigo et al., 2021), as found in congenital cerebellar malformations (CM). Indeed, the neuropsychological profile of children and adults with CM shows symptoms which overlap with the CCAS profile described in adults with acquired cerebellar lesions (Pinchefsky et al., 2019; Tavano & Borgatti, 2010).

The underneath mechanisms of the wide spectrum of CCAS symptoms might be linked to the cerebellar role in predictive control. The cerebellum is thought to contribute in creating and controlling adaptive models of the environment. This would be exerted by integrating internally stored representations with external stimuli to fine-tune the performance according to the contextual demands (Koziol et al., 2014).

Within the frame of social cognition, the cerebellum would process others' action to predict the intention behind the observed body kinematics as a forward model, by generating feedback predictions of the observed movements and transforming them into a simulated motor pattern (Gazzola & Keysers, 2009; Wolpert et al., 2003). This operation would support the prediction of upcoming actions, which is crucial for efficient everyday social interactions. Accordingly, neuroimaging evidence has demonstrated cerebellar activation during action observation (Raos & Savaki, 2021). Nevertheless, the processing of body kinematics alone may not be sufficient to generate correct predictions about other people's intentions/actions.

According to predictive coding accounts (Kilner, 2011), bottom-up sensorial information (e.g. body kinematics) need to be combined with top-down expectations (priors), formed through the experience of the statistical regularities that are inherent in the natural world (Huang & Rao, 2011). In this vein, the context in which a given action is often embedded can provide a prior supporting action prediction. Top-down priors have been demonstrated to bias action recognition as well as to modulate motor activation during action observation (Amoruso et al., 2018; Betti et al., 2022; Bianco et al., 2020; see Amoruso & Finisguerra, 2019 for a review).

Recent clinical studies assessed the impairment of social prediction abilities in congenital or acquired CM (Butti et al., 2020b; Urgesi et al., 2021). Patients with non-progressive CM were impaired in leveraging on contextual information to predict others' actions (Urgesi et al., 2021). In these studies, the probability of co-occurrence between a particular social/physical events and contextual elements was manipulated in an implicit-learning phase aiming at creating highly or moderately informative expectations. The use of expectations was then tested by asking participants to predict the unfolding of the social/physical events in situations of perceptual uncertainty due to a temporal occlusion, which prompted the observer to leverage on contextual expectation to respond. Compared to healthy controls and control patients without CM, CM patients did not benefit from contextual expectations to predict actions. Notably, this impairment was significantly associated with social cognition abilities. With the same task, a previous work documented the very same impairment also in children with a brain tumor affecting the cerebellum, but not supratentorial areas (Butti et al., 2020b). These findings conform with the idea that the impairment of cerebellar patients in social perception may be explained by an impairment of predictive processing (Sokolov, 2018; Stoodley & Tsai, 2021).

Other studies have assessed the effects of neuromodulation of cerebellar activity on the same functions. In particular, the involvement of the cerebellum in motor and non-motor functions has been increasingly investigated by means of transcranial electric stimulation techniques (tES) (Grimaldi et al., 2014; van Dun et al., 2017). Among these techniques, the cerebellar transcranial direct current stimulation (ctDCS) has been demonstrated to modulate cerebellar cortical excitability (Galea et al., 2009) and behavior (Oldrati & Schutter, 2018). The tDCS delivers a continuous, weak electrical current typically using a bipolar montage with an active electrode located over the targeted region – below the inion in case of ctDCS – and a reference electrode located over a cephalic or an extracephalic site (e.g., the deltoid or the buccinators muscles, commonly targeted as reference areas in ctDCS) (Ferrucci et al., 2015; Parazzini et al., 2014). This technique alters spontaneous brain activity, modulating the resting state potential of the neural population in the vicinity of the electrodes (Stagg et al., 2018).

By integrating cerebellar functions in a predictive processing framework, a recent study investigated the use of contextual expectations to interpret ambiguous sensory sceneries by means of ctDCS in healthy adults (Oldrati et al., 2021). The same experimental tasks as in Butti and colleagues' (Butti et al., 2020b) and Urgesi and colleagues' (Urgesi et al., 2021) studies were adopted. Here (Oldrati et al., 2021), the stimulation was found to modulate the ability of the participants to predict social actions but not physical events. While the inhibitory (cathodic) stimulation hampered the ability to predict actions embedded in highly informative contexts, the facilitatory (anodic) stimulation was found effective in boosting the prediction of actions embedded in moderately, but not highly, informative contexts. Overall, these findings, while supporting the role of the cerebellum in social prediction, also encouraged the use of ctDCS in a rehabilitative perspective to boost social competences.

It is unclear, however, whether and how the effects of ctDCS may be altered by micro- or macro-structural malformation of the cerebellum, as observed in CM. Indeed, a difficulty in predicting clear polarity-dependent effects of cerebellar, compared to cerebral, tDCS has been highlighted in the general population (Oldrati & Schutter, 2018), likely due to the highly convoluted cerebellar structure and the individual variability in anatomy and neurophysiological constitution of cerebellar circuitry (Luft et al., 1999; Raz et al., 2001). This is even more problematic for patients with CM, where structural defects may alter the magnitude, orientation, and location of current density distributions (Wagner et al., 2007). To the best of our knowledge, no previous study has used tDCS in patients with non-progressive, congenital CM. A few recent clinical trials (Benussi et al., 2017, 2018, 2021; Maas et al., 2022; Maas & van de Warrenburg, 2023) addressed the neuro-restorative effects of tDCS in patients with progressive, hereditary ataxia, reporting contrasting results of improvement of CCAS symptoms.

Considering the impairment in social predictive processes in either acquired or congenital CM (Butti et al., 2020b; Urgesi et al., 2021), and in light of previous evidence of ctDCS effects in modulating the ability to predict social actions in condition of perceptual ambiguity (Oldrati et al., 2021), this study aimed at verifying whether such effect could be replicated in a sample of patients with non-progressive, congenital CM. In a rehabilitation perspective, here we tested exclusively the effect of the anodic stimulation, associated with positive effects as opposed to the cathodic stimulation, on the prediction of social action in a sham-controlled design. Specifically, anodic ctDCS was expected to boost the ability of patients to leverage on moderately informative priors to predict unfolding actions as compared to sham stimulation.

2. Method

2.1. Participants

Thirty-three adolescents and young adults with congenital, non-progressive CM, counseled at the IRCCS E. Medea, were screened against inclusion/exclusion criteria and considered recruitable. Inclusion criteria were: i) a diagnosis of congenital, non-progressive CM as revealed by T1- and T2-weighted images obtained through MRI; ii) age ≥11 and ≤30 years old. The main inclusion criterion was primarily neuroradiological, focusing on morphological aspects without considering the manifestation of clinical symptoms related to cerebellar dysfunction. We applied this radiological criterion without imposing any size restrictions on the cerebellar malformation. Exclusion criteria were: i) contraindications to tDCS administration (e.g., epilepsy, metal implant, pacemaker, migraine, see supplementary material); ii) comorbidity with neurodevelopmental disorders, irrespective of clinical scoring falling within the minimum or maximum impairment range; iii) presence of severe sensory or motor deficits that could impede the execution of the task, as evaluated clinically. To rule out that the presence of autistic traits could confound the effects on the task, participants filled out the age-appropriate, Italian versions of the Autism-Spectrum Quotient questionnaire (AQ) (Baron-Cohen et al., 2001). Once recruited, patients or, if minors, their legal guardians filled out a questionnaire to confirm the suitability for tDCS administration.

The sample size was estimated based on the effect size of the interaction between the factors stimulation (anodic vs. sham) and expectancy (high vs. low) calculated from the data collected in our previous study (Oldrati et al., 2021). The analysis conducted with G*Power (Faul et al., 2007) indicated that for a 2×2×2 repeated-measures analyses of variance (RM-ANOVA) design (numerator df = 1), by setting the expected effect size f(U) = 0.7 (as in SPSS option), the alfa threshold of $p = 0.05$ and the desired power (1 - β) at 0.8, 19 participants were sufficient to detect the effects of interest. Twenty patients consented to participate in the study (60.6 % of the recruitable patients) and were enrolled to comply with eventual drop-outs (5 %). One patient was excluded from data analysis as she performed the task at chance level. Another patient was excluded as he obtained an AQ score above the clinical threshold, (i.e., a total score ≥32, as suggested in Baron-Cohen et al., 2001). This patient was excluded due to the potential confounding effect that autistic traits may have exerted on his ability to perform the task (Amoruso et al., 2019).

The final sample included 18 patients (age range 11–29; mean age = 15.7, SD = 5.2 years; 4 F/14 M). Patients' Intelligence Quotient (IQ) (mean = 72.1, SD = 25.9) was assessed by means of age-corresponding Wechsler Intelligence Scale (Wechsler, 2003). Fig. 1 schematizes the diagnostic composition of the sample (see supplementary material for detailed clinical descriptions; for more detailed information on the diagnosis of the molar tooth sign, please refer to D'Abrusco et al., 2022). Written informed consent was obtained from all adult participants. For minors written consent was obtained from their legal guardians. Verbal consent was obtained from all patients before starting the experiment. The study was approved by the local ethical committee and conducted in accordance with the Declaration of Helsinki.

2.2. Procedure and task

The study adopted a single-blind, sham-controlled, within-subjects design. Participants performed a social prediction task while receiving either real or sham stimulation. Real or sham stimulation were applied in separate sessions, lasting approximately 40 min and scheduled at least 24 h apart to ensure a wash-out period. The order of stimulation conditions was counterbalanced between patients. At the end of each session, participants were asked to rate from 0 to 10 the level of discomfort they experienced during the stimulation on a 10-cm Visual Analogue Scale (VAS). Furthermore, a modified version of a questionnaire for evaluating tDCS-induced sensations (Fertonani et al., 2015) was administered (see supplementary material).

The action prediction task was adapted from previous studies (see Amoruso et al., 2019; Bianco et al., 2020; Oldrati et al., 2021 for detailed descriptions). Participants were required to observe videos of a child grasping an apple or a glass to perform either individual (i.e., eating/drinking) or interpersonal actions (i.e., giving the object to a peer sitting in front of the child). Each action was performed in presence of a specific contextual cue: a violet- or an orange-colored dish for the actions performed toward the apple; a white- or a blue-colored tablecloth for the actions performed with the glass. Since videos were interrupted before their completion, participants were asked to predict action unfolding (i.e., individual or interpersonal) in a two-alternative forced choice mode. The task comprised a familiarization (2 blocks) and a testing phase, each repeated twice (Fig. 2A).

The aim of the familiarization phase was to establish an arbitrary association between a contextual cue and a given action (Fig. 3A), in order to create different levels of expectancy of an action given a contextual cue. To this aim, during the familiarization phase the videos representing each action-contextual cue associations were presented for an unequal number of trials. Particularly, in a high-expectancy condition, an individual action (e.g., reaching to eat/drink) towards a specific object (e.g., apple) was presented in the 90 % of trials with a contextual cue (e.g., orange-colored plate) and only in the 10 % of trials with the other (e.g., violet-colored plate). This association was inverted for the interpersonal action (i.e., reaching to offer) performed towards the same object (i.e., grasping to offer the apple presented in the 90 % of trials with a violet-colored plate and in 10 % of the trials with an orange-colored plate). Conversely, a low-expectancy condition was used for the other object (e.g., glass), for which individual actions were presented in the 60 % of trials with a given contextual cue (e.g., white-colored tablecloth) and in the remaining 40 % of trials with the other contextual cue (e.g., blue-colored tablecloth). The opposite association was used for the interpersonal action on the same object (e.g., grasping to

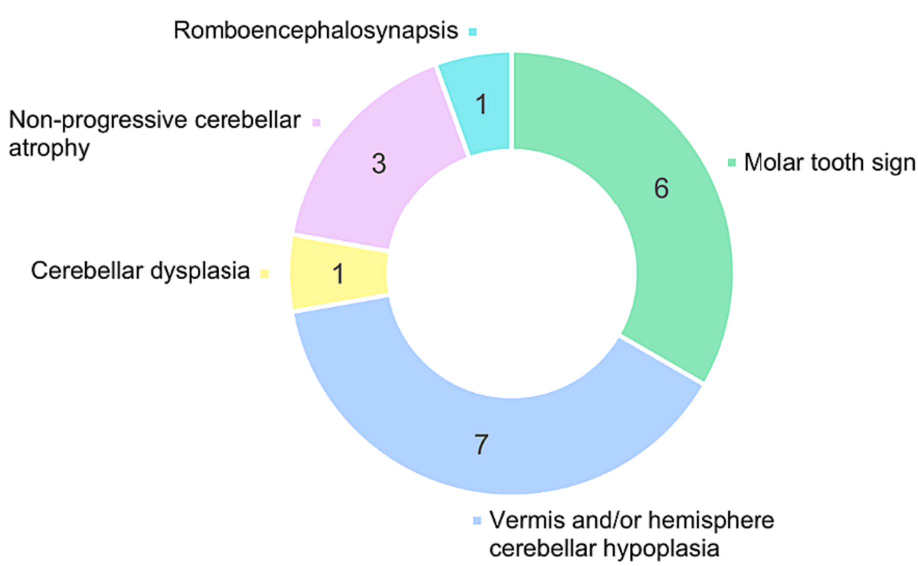

Fig. 1. Circular percentage graph reporting the number of participants for each cerebellar malformation type in the tested sample. P14, diagnosed with molar tooth sign and dysplasia, was included in the molar tooth sign group.

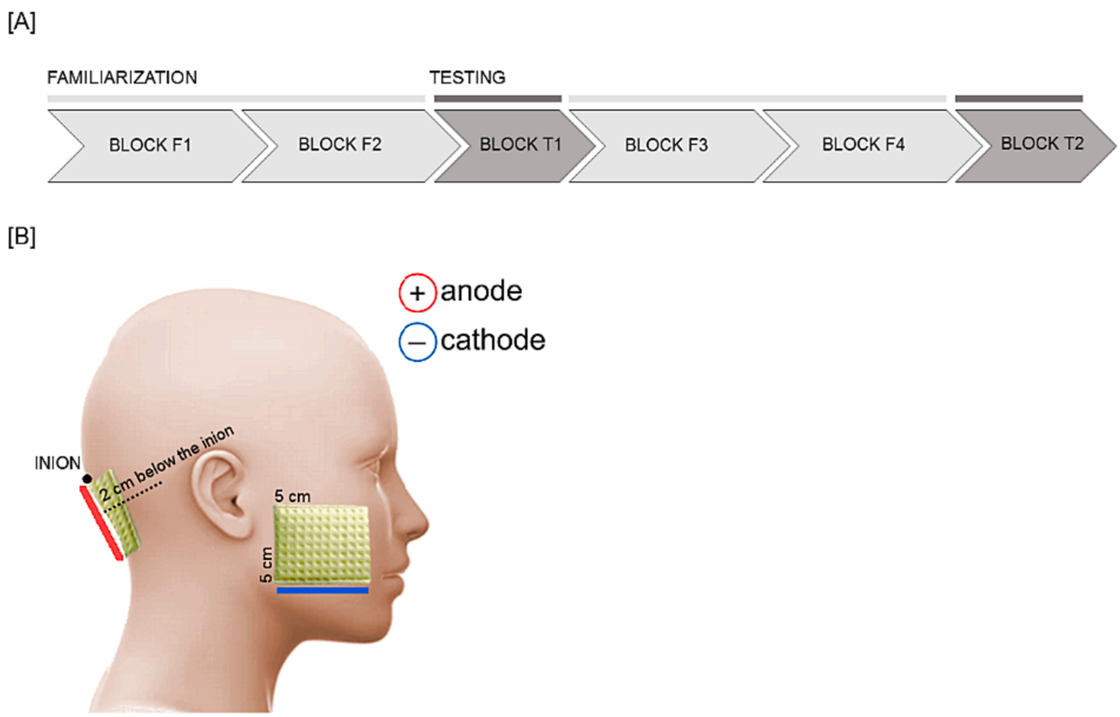

Fig. 2. A: task structure; B: schematic depiction of the placement of electrodes for anodic ctDCS with the anode (red) over the medial cerebellum and the cathode (blue) over the right buccinator muscle. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

offer the glass was presented 60 % of trials with a blue-colored tablecloth and 40 % of trials with a white-colored tablecloth). Thus, within the two levels of expectancy, each action was associated with high probability (i.e., 90 or 60 %) to a contextual cue and with low probability (i.e., 10 or 40 %) to the other (Fig. 3B). This probabilistic associative learning was expected to trigger the formation of contextual priors about the unfolding action, that was expected to serve action prediction in the following testing phase. Importantly, the contextual prior was more informative about action unfolding in the high- than in the low-expectancy condition. The association between action and contextual cue was counterbalanced across participants and different action-cue associations were used in the two sessions for each participant, to reduce repetition effects.

In the familiarization phase, videos were interrupted after 833 ms of presentation (i.e., 25 frames), which corresponded to two frames before the actor made full contact with the target object. Differently, in the testing phase, videos were interrupted after 500 ms of presentation (i.e., 15 frames), occluding most of the hand pre-shaping that could inform on how to differentiate between the two actions. This way, we created a condition of perceptual uncertainty that allowed us to test the ability to retrieve and/or use the previously formed contextual prior expectations.

In both phases, trials started with a fixation cross of 3000 ms, followed by video-clip presentation. After (in the familiarization phase) or at the onset (in the testing phase) of the video-clip, the labels (in Italian) of the two possible actions (i.e., 'to eat'/'to drink' and 'to give') were presented on the right/left bottom part of the screen, and remained on the screen until a response was recorded. Participants provided their response, without any time constraints, by pressing with the index finger the keys 'z' or 'm' (for left or right choices). The location of the labels was counterbalanced between participants. An empty black screen was presented for 1,000 ms between consecutive trials. The videos were displayed at a rate of 30 Hz (i.e., 33.33 ms per frame). They were presented on a black background on a 17″ monitor (refresh frequency, 60 Hz; resolution 1366×768) and subtended a 15.96°×11.97° region viewed from a distance of 60 cm. The task was built in E-Prime 2 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Fig. 3B provides a schematic representation of the task.

2.3. tDCS parameters and application

The stimulation protocol applied here was as that used in a previous study with healthy participants (see Oldrati et al., 2021 for details). tDCS was delivered by a battery-driven constant DC current stimulator (BrainStim, EMS s.r.l., Bologna, Italy), using two 5×5 electrodes (25 cm^2) - current density: 0.06 mA/cm^2 - inserted in a synthetic sponge covered with conductive gel. The current intensity was set at 1.5 mA, in accordance with the safety guidelines for the administration of tDCS on the pediatric population (Antal et al., 2017). Either in the real (anodic) or in the sham stimulation condition, the active electrode was centered over the medial cerebellum – 2 cm below the inion with electrode's lateral borders 2 cm medially to the mastoid apophysis - whereas the reference electrode was placed over the right buccinator muscle (Fig. 2B). In the anodic stimulation condition, the stimulation was ramped down (ramping period: 30 s) after 20 min of tDCS. In the sham condition, the stimulation was turned on only for 60 s at the beginning and at the end of the stimulation period. The order of stimulation conditions (anodic vs. sham) was counterbalanced between participants.

2.4. Data handling and statistical analysis

The proportion of correct responses (accuracy) for each experimental condition was analyzed. In keeping with previous studies (Amoruso et al., 2019; Betti et al., 2022; Bianco et al., 2020; Butti et al., 2020b; Oldrati et al., 2021; Urgesi et al., 2021), accuracy in action prediction was coded based on the kinematics, regardless of the intention suggested by the contextual cues. Experimental conditions were the following: STIMULATION type (anodic vs. sham), EXPECTANCY (high 10 and 90 % vs. low 40 and 60 % - predictability of the contextual cue) and PROBABILITY (high 60 and 90 % vs. low 10 and 40 % action-cue association). Data extracted in the testing phase was filtered based on response times (RTs). Trials with RTs exceeding of ±2.5 SD the mean value calculated within subject, stimulation type, expectancy and probability conditions

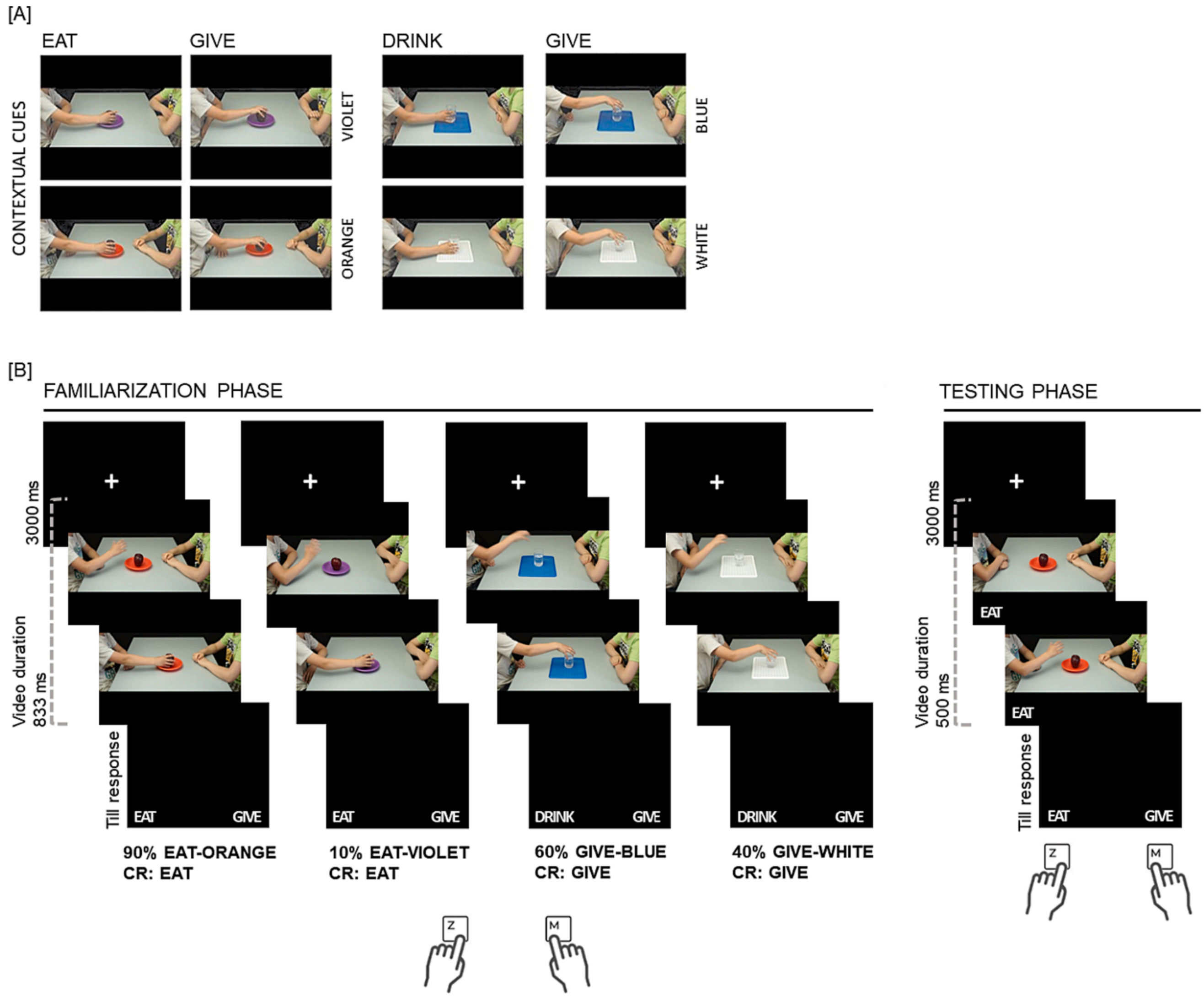

Fig. 3. A: Examples of the experimental stimuli. B: Examples of trials in the familiarization and testing phases. In one of the 8 possible versions, the high expectancy condition was assigned to the pair of actions directed to the apple, while the low expectancy condition was assigned to the pair of actions directed to the glass. In particular, the 90% of apple-action trials displayed a grasping-to-eat action from an orange plate or a grasping-to-offer action from a violet plate (high expectancy–high probability). The opposite action-cue associations were presented in the remaining 10% of apple-action trials (high expectancy–low probability). This way, an orange- or a violet-colored plate strongly biased, respectively, to grasping-to-eat or to grasping-to-offer actions. For what concerns the actions directed to the glass, 60% of trials displayed a grasping-to-offer action from a blue-colored tablecloth or a grasping-to-drink action from a white-colored tablecloth (low expectancy–high probability). The opposite intention-cue associations were presented in the remaining 40% of trials (low expectancy–low probability). This way, a blue colored tablecloth moderately biased to grasping-to-offer and a white one to grasping-to-drink. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

were deleted. In total, 46 trials (2.9 %) were deleted in the anodic condition and 50 (3.2 %) in the sham condition. A chi-square test confirmed that the proportion of deleted trials was comparable among conditions ($X_3 = 0.32$, $p = 0.96$). Two participants exhibited a significant loss of attentive focus and high distractibility in the second half of the task (i.e., blocks F3, F4 and T2 – see Fig. 2A). This was confirmed by inspection of the mean accuracy obtained in these blocks, in which a drop in performance greater than 40 % was detected compared to the first half of the task. The F3, F4 and T2 blocks of these two participants, performed during both the anodic and sham stimulation, were excluded from the analysis.

First, a 2 × 2 repeated-measures analysis of variance (RM-ANOVA) was conducted on accuracy extracted from the familiarization phase, with the factor STIMULATION and EXPECTANCY as within-subject variables. The PROBABILITY condition was not considered in analyzing the familiarization phase because of an inherently different number of trials. Next, a 2 × 2 × 2 RM-ANOVA was conducted on accuracy extracted from the testing phase, with the factor STIMULATION, EXPECTANCY and PROBABILITY as within-subject variables. Latencies of responses were not entered into the analyses, since clumsiness and motor coordination difficulties, typical of this clinical population, may have influenced response times, making them an unreliable measure.

Additionally, based on the results of the 2 × 2 × 2 RM-ANOVA, in order to identify potential predictors of the response to the intervention, we calculated a % delta value (i.e., the accuracy gain index) for each individual. This was obtained by subtracting the accuracy for low-expectancy trials achieved during anodic stimulation from that obtained during sham stimulation, and then dividing the result by the second term (i.e., (Anodic-Sham)/Sham*100). This way, positive values indicate a gain in accuracy during the anodic condition, with respect to the sham. Subsequently, we conducted a series of Pearson's correlations between the accuracy gain index and various variables, including:

demographic factors (age), neuropsychological metrics (IQ, scaled scores from the Visual Attention, Theory of Mind, and Affect Recognition subscales of the NEPSY-II battery) and clinical parameters (subscales and total score of the Autistic Quotient questionnaire) (see supplementary material for a description of the neuropsychological and clinical measures).

Lastly, we performed a dependent-sample *t*-test on the VAS scores during anodic vs. sham stimulation condition to rule of the potential confounding effect exerted by differences in the perceived tDCS-induced sensations across conditions.

Statistical analyses were performed using STATISTICA 8.0 (StatSoftInc, Tulsa, Oklahoma). Data are reported as mean (M) ± standard error of the mean (SEM). The level of statistical significance in all tests was defined as $p < 0.05$. Duncan post hoc tests were performed to follow-up significant interactions and correct for multiple pair-wise comparisons. Effects sizes were reported as partial eta squared (η_p^2) for the RM-ANOVAs and as Cohen's *d* for significant effects and the follow-up pairwise comparisons.

3. Results

Visual inspection of data confirmed that all the patients included in the analysis performed the task adequately (Fig. 4A). The analysis on the mean accuracy in the familiarization phase did not yield any significant effect (all $p > 0.3$). The analysis on accuracy in the testing phase showed a significant interaction effect of STIMULATION × EXPECTANCY ($F_{1,17} = 6.39$, $p = 0.02$, $\eta_p^2 = 0.27$). Post-hoc analyses highlighted that participants were more accurate in predicting action unfolding during anodic (M = 0.84; SEM = 0.03) with respect to sham ctDCS (M = 0.78, SEM = 0.03) in the low-expectancy condition ($p < 0.01$, $d = 0.42$). Conversely, in the high-expectancy condition, performance did not differ between stimulation types (anodic: M = 0.84, SEM = 0.03; sham: M = 0.85, SEM = 0.03; $p = 0.6$, $d = 0.06$) (Fig. 4B). Thus, the results suggested a polar-, expectancy dependent effect of ctDCS on context-based action prediction. A significant difference in accuracy between the two expectancy conditions emerged during sham stimulation ($p = 0.004$, $d = 0.48$), indicating greater accuracy in high- than low-expectancy trials. In contrast, this difference was not significant during the anodic stimulation ($p = 1$; $d = 0.002$, Fig. 4B), likely reflecting the enhancement effect induced by anodic ctDCS for the low-expectancy trials. No other significant main effects or interactions were observed (all $p > 0.13$).

Moreover, a post-hoc analysis was conducted to refine our understanding of the accuracy gain resulting from the stimulation within each malformation group. The accuracy gain index, described above, served as the basis for this analysis, and its median value was employed as a threshold. Patients with an accuracy gain below the threshold were categorized as "less gainers" while those equal to or exceeding the threshold were labeled as "more gainers". In the molar tooth sign group, one patient (17 %) fell into the "less gainers" category, while the remaining 5 (83 %) were classified as "more gainers". In the vermis and hemisphere hypoplasia group, 4 patients (57 %) were identified as "less gainers", and the remaining 3 (43 %) as "more gainers". In the cerebellar atrophy group, 2 patients (67 %) were categorized as "less gainers", and only one (33 %) was labeled as "more gainer". Lastly, the single patient with romboencephalosynapsis and the one with cerebellar dysplasia were both classified as "more gainers".

Overall, this suggest that "more gainers" prevailed in the molar tooth sign group. Except from the patients with hypoplasia and atrophy that seem to be equally distributed between the "less gainers" and "more gainers" categories, advantage from stimulation seems to be consistent across malformation types. The bottom panel of Fig. 4 illustrates the accuracy gain for each patient, color-coded by malformation type (Fig. 4C).

Table 1 reports accuracy scores for each level of probability across stimulation conditions.

The correlation analysis showed that none of the correlations between the accuracy gain index and the selected demographic/clinical measures reached statistical significance (see Table 2).

Lastly, regarding the evaluation of the tDCS-induced sensations, a dependent-sample *t*-test on the VAS scores obtained after real vs sham stimulation yielded a non-significant result ($t_{17} = 0.27$, $p = 0.79$, $d = 0.06$), suggesting that participants were blinded to the stimulation condition.

4. Discussion

Previous studies showed an impaired use of previous experience for the prediction of social events in acquired (Butti et al., 2020b) or congenital (Urgesi et al., 2021) CM. Based on these results, and after documenting the positive effects of ctDCS in boosting the reliance on prior for social prediction in healthy adults (Oldrati et al., 2021), here, we tested whether anodic ctDCS would enhance context-based prediction of others' action in a sample of adolescents and young adults with non-progressive, congenital CM. To this aim, patients were presented with a social prediction task, during the administration of anodic or sham ctDCS. In a learning phase, the association between actions and contextual elements was manipulated in terms of their probability of co-occurrence, to create highly or moderately informative expectations. Then, in a testing phase, patients were evaluated for their ability to predict the upcoming actions in conditions of reduced sensory evidence, obtained by a temporal-occlusion paradigm. The working hypothesis was a boosting effect of anodic vs. sham ctDCS on action prediction in moderately informative contexts (Oldrati et al., 2021). This hypothesis was confirmed. Indeed, during sham stimulation, we found that patients were less accurate in recognizing the unfolding action in a moderately informative context compared to when embedded in a highly informative one, while during anodic stimulation, they became as accurate to predict actions in moderately as in highly informative contexts.

Here we found a polar dependent effect of the stimulation on patients' ability in using prior for action prediction. As observed in the preceding study on healthy adults (Oldrati et al., 2021), this is in accordance with the conventional supposition that the excitation effect of the anodic stimulation on cortical activity would be associated with improving behavioral effects (Galea et al., 2009). Moreover, the improvement we observed for moderately- but not for highly-informative conditions, suggests a state/expectancy dependent effect of ctDCS. It can be hypothesized that this effect is influenced by the different levels of activation of the cerebellar networks during the prediction of actions embedded in moderately- or highly-informative contexts, which could lead to lower or higher levels of cerebellar activation, respectively. There is evidence that the cerebellum, during a sentence completion task, is more active and differently susceptible to ctDCS after presentation of strong than weak contextual cues to the missing word (D'Mello et al., 2017). We speculate that, in high-expectancy trials, the level of (higher) cerebellar activation could not be further boosted by ctDCS, yielding a null effect of the stimulation. On the other hand, in low-expectancy trials, the level of (lower) cerebellar activation could be further enhanced by the stimulation, leading to the behavioral improvement.

In general, cerebellar tES has been demonstrated to effectively modulate a range of socio-cognitive (Clausi et al., 2022; Ferrari et al., 2018; Ferrari et al., 2019, 2022; Ferrucci et al., 2012) and affective functions (Schutter & Van Honk, 2009; see Cattaneo et al., 2022 for a review) in the healthy population and brain stimulation techniques have been administered to reduce socio-affective symptoms in cerebellar diseases (Benussi et al., 2021; Maas et al., 2022) and neuropsychiatric disorders (van Dun et al., 2022). However, to the best of our knowledge, this is the first brain stimulation study aiming at boosting social prediction abilities in non-progressive, congenital CM. The potential applications of ctDCS goes beyond the specific population of this study. Indeed, the impairment of cerebellar-mediated predictive mechanisms

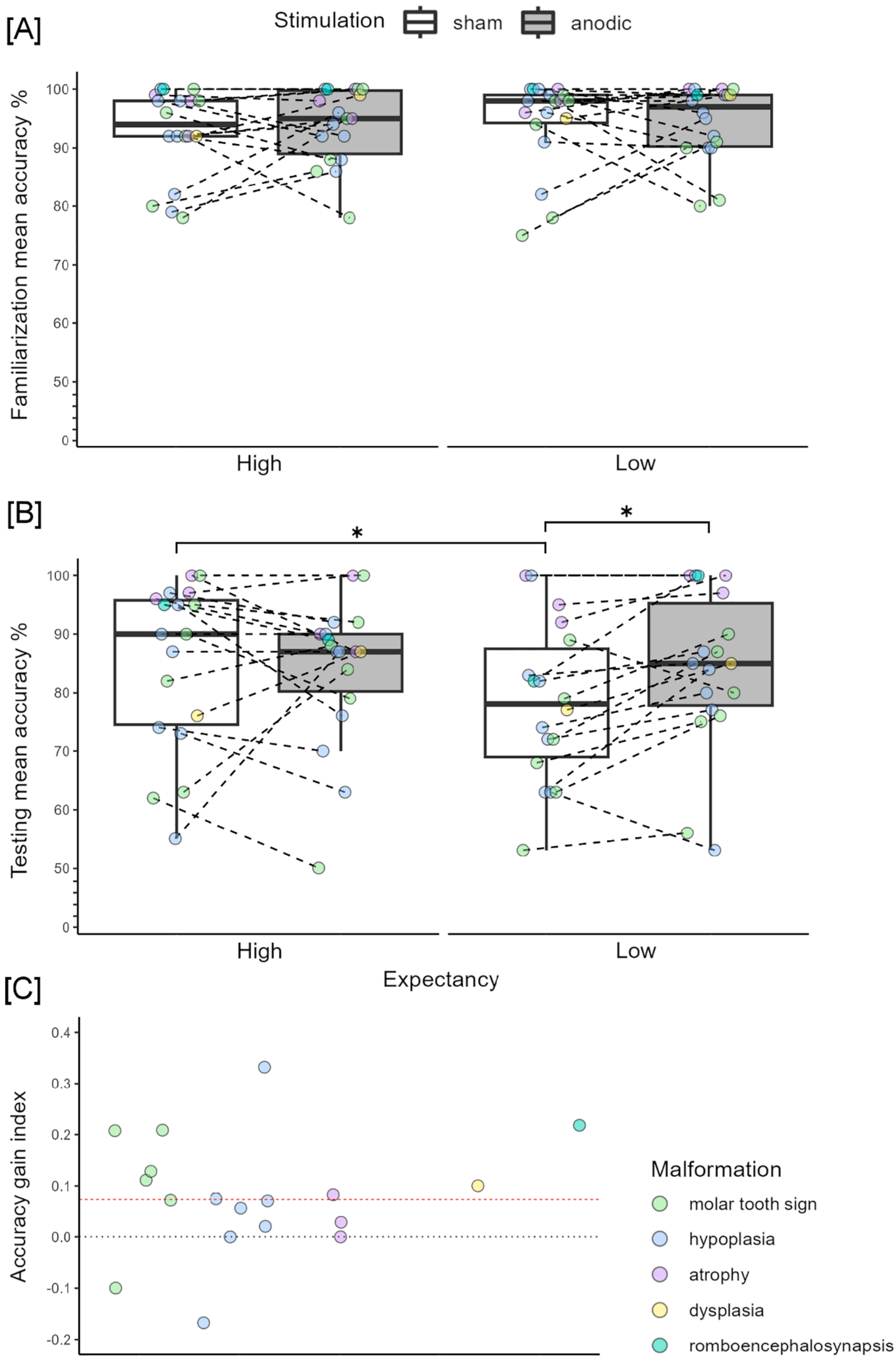

Fig. 4. Box plot displaying the accuracy (% of correct responses) obtained in the familiarization [A] and testing phase [B], during sham (white) and anodic (gray) stimulation and as a function of the level of expectancy (high vs. low). Points represent individual observations, color-coded by malformation type. Dashed lines connect observations belonging to the same patient across stimulation conditions. Panel [C] displays individual data points of the accuracy gain index, color-coded by malformation type. The red dashed line signals the median value (0.07), serving as a threshold to classify patients into the "less gainers" or "more gainers" category. The gray dashed line is set at the value of 0, with observations falling below indicating no improvement. *$p < 0.05$.

Table 1
Mean (SE) of accuracy scores for each level of probability across stimulation condition.

	Low expectancy		High expectancy	
Probability	**40 %**	**60 %**	**10 %**	**90 %**
anodic	0.83 (0.02)	0.84 (0.02)	0.83 (0.02)	0.84 (0.02)
sham	0.80 (0.02)	0.75 (0.02)	0.86 (0.02)	0.83 (0.02)

Table 2
Mean (SD) and min/max range of the selected demographic/clinical measures, Pearson's correlations coefficients and uncorrected p-values.

Measures	Mean (SD)	Min/max range	r	p
Age (in years)	15.7 (5.2)	11–29	−0.09	0.72
IQ	72.1 (25.9)	37–137	−0.21	0.4
NEPSY-II battery				
VA	4.7 (3.9)	1–13	−0.05	0.85
ToM	5.4 (4.1)	1–14	0.08	0.75
AR	5.5 (3.9)	1–14	0.06	0.82
AQ questionnaire				
Social skill	3.3 (1.8)	0–6	−0.25	0.31
Attention switching	4.7 (2.1)	2–9	−0.43	0.08
Attention to detail	2.8 (1.9)	0–8	0.19	0.46
Communication	3.7 (1.9)	0–7	0.13	0.6
Imagination	4.8 (1.9)	2–9	−0.23	0.37
Total score	19.4 (3.8)	12–26	−0.31	0.21

Abbreviations: Visual Attention (VA), Theory of Mind (ToM) and Affect recognition (AR).

may be the leading cause of social dysfunction in various neuropsychiatric conditions marked by distinct levels of cerebellar anomalies. These conditions include autism spectrum disorder (Stoodley & Tsai, 2021) developmental coordination disorders (Debrabant et al., 2013), and psychotic disorders (Moberget & Ivry, 2019). Furthermore, the exploration of cerebellar stimulation in pathological conditions linked to cerebellar abnormalities may pave the way for the development of innovative treatment protocols for patients with hereditary ataxia, particularly in the socio-affective domain (Ciricugno et al., 2024).

Social predictions require the integration of prior knowledge about an individual or a situation into a mental representation that must be adaptable in face of a changing environment (Brown & Brüne, 2012). According to a supervised error-based paradigm of cerebellar learning (Hull, 2020), the prediction error mechanism encoding discrepancies between expected and incoming inputs is crucial to update predictive models in order to enable a fluid, well-timed, appropriate response. The extensive cortico-cerebellar-cortical connectivity would allow for cerebellar predictive modeling to be applied to different types of social information. Accordingly, a failure of predictive models is thought to underlie breakdowns in social communication and deficits in social behaviors in a variety of cerebellar disorders (Schmahmann et al., 2007). In keeping with this idea, a virtual-reality rehabilitation program for children with CM has been developed to improve social predictive abilities by training the use of context-based expectations (Butti et al., 2020a; Urgesi et al., 2021).

Fostering the use of internal models of social events is expected to yield positive outcomes in everyday life situations, potentially leading to improvements in the social and affective well-being of patients and their families. The level of social cognition impairment observed in patients with cerebellar pathologies has been likened to that seen in autism or schizophrenia, significantly impacting patients' quality of life (Karamazovova et al., 2023). Exploring how ctDCS can boost the effects of social rehabilitation during developmental stages may open avenues to reactivate plasticity mechanisms, even in chronic conditions where the benefits of functional rehabilitation alone may be limited, as in the clinical population examined in the present study. Further, adopting an integrative rehabilitation approach, which combines functional training with non-invasive brain stimulation, could enhance intervention efficacy, optimizing the collaborative efforts of clinicians and patients.

Importantly, tDCS has demonstrated a good safety profile for neurological disorders (Antal et al., 2017). Moreover, the participation rate observed in this study seems to confirm the positive attitude towards tDCS and its potential application in rehabilitation.

The present findings must be interpreted in light of some limitations. First, the sample size was modest. Despite this, the effect size of the main result cannot be considered negligible. The use of a single-blind design must be acknowledged as another limitation. Alongside the broad age-range, another limitation is the heterogeneity of the clinical features of the sample, in terms of level of intellectual functioning, types of cerebellar malformation and underlying etiology. Indeed, extending beyond specific cerebellar pathologies, cerebellar ataxias constitute a diverse spectrum of disorders. This diversity is evident in terms of phenotypes, disease mechanisms and symptoms (Manto et al., 2020). Given this heterogeneity, an important issue is that distinct cerebellar pathologies may preferentially damage different parts of cerebellar circuitry and thus produce variable responses to brain stimulation protocols (Manto et al., 2021). This highlights the necessity for employing tailored montage solutions for cerebellar stimulation to enhance stimulation focality. If concern holds significance in the context of targeting cerebral regions with tES, it becomes even more crucial for cerebellar stimulation, due to the intricate structure of the cerebellar cortex, especially in conditions marked by heightened atrophy or alterations in sulci width (Ciricugno et al., 2024). Moreover, both in vitro (Radman et al., 2009) and computational modeling studies (Zhang et al., 2021) have indicated that Purkinje cells, the predominant neuron type in the cerebellum, exhibit heightened sensitivity to tDCS. Intriguingly, varying degrees of Purkinje cell loss have been documented in distinct spinocerebellar ataxias (Louis et al., 2019), potentially influencing outcomes in trials employing tES protocols.

Differences in ctDCS-protocol outcomes are likely to depend also on what can be referred to as "cerebellar reserve". Analogously to the classical definition of "reserve", the cerebellar reserve refers to the capacity of the cerebellum to compensate and restore function in response to pathology and it can influence the possibility to benefit from the administration of tES targeting the cerebellum (Mitoma et al., 2020). Cerebellar restoration and compensation, depending on the underlying etiology, may occur through functional reorganization and by strengthening synaptic plasticity. Thus, when the capacity for functional reorganization is preserved, neuromodulation may represent a therapeutic option to facilitate cerebellar reserve. However, further research is still needed to verify the clinical efficacy of cerebellar tES, also taking into account the level of cerebellar reserve characterizing distinct diagnoses (Manto et al., 2021). Future research, enrolling larger numbers of patients, is warranted to pinpoint demographic or clinical characteristics—such as severity of cerebellar symptoms as measured with appropriate scales for the evaluation of cerebellar dysfunction —that could serve as potential predictors of the likelihood to benefit from this intervention or similar ones.

Moreover, while our study consisted of a one-shot experiment with only one real-stimulation session, we acknowledge that a multi-session approach may have a cumulative dose effect of the stimulation and, thus, enhance the intervention's efficacy by inducing long-term effects. In keeping with this view, studies testing the effects of multiple ctDCS sessions in patients with cerebellar ataxia reported significant and lasting improvement in motor symptoms and physiological cerebellar brain inhibition pathways (Benussi et al., 2017, 2021; Pilloni et al., 2019; but see Maas et al., 2022), suggesting that a multi-session approach may lead to the strongest clinical benefit. Of note, by considering that optimal effects of brain stimulation are often achieved when combined with other behavioral trainings (Antonenko et al., 2023), the integration of a multiple ctDCS-session with social prediction trainings with virtual reality (Butti et al., 2020a; Urgesi et al., 2021) might boost generalization and long-term effects of the treatment.

Despite the limitations, the expectancy-dependent effect of anodic ctDCS confirmed the results of a preceding study on healthy adults. Further, the present results encourage the exploration of ctDCS as a means to boost social predictive abilities, alone or in combination with other interventions (Butti et al., 2020a; Urgesi et al., 2021), in disorders with cerebellar anomalies.

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CRediT authorship contribution statement

Viola Oldrati: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Niccolò Butti:** Writing – review & editing, Investigation, Data curation. **Elisabetta Ferrari:** Writing – review & editing, Investigation, Data curation. **Sandra Strazzer:** Writing – review & editing, Methodology. **Romina Romaniello:** Writing – review & editing, Methodology, Data curation. **Renato Borgatti:** Writing – review & editing, Methodology. **Cosimo Urgesi:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Alessandra Finisguerra:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets presented in this study can be found at: Zenodo repository, https://doi.org/10.5281/zenodo.10715417.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2024.103582.

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