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Anodal cerebellar stimulation increases cortical activation: Evidence for cerebellar scaffolding of cortical processing

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Abstract

While the cerebellum contributes to nonmotor task performance, the specific contributions of the structure remain unknown. One possibility is that the cerebellum allows for the offloading of cortical processing, providing support during task performance, using internal models. Here we used transcranial direct current stimulation to modulate cerebellar function and investigate the impact on cortical activation patterns. Participants ($n = 74$; 22.03 ± 3.44 years) received either cathodal, anodal, or sham stimulation over the right cerebellum before a functional magnetic resonance imaging scan during which they completed a sequence learning and a working memory task. We predicted that cathodal stimulation would improve, and anodal stimulation would hinder task performance and cortical activation. Behaviorally, anodal stimulation negatively impacted behavior during late-phase sequence learning. Functionally, we found that anodal cerebellar stimulation resulted in increased bilateral cortical activation, particularly in parietal and frontal regions known to be involved in cognitive processing. This suggests that if the cerebellum is not functioning optimally, there is a greater need for cortical resources.

KEYWORDS
cerebellum, functional magnetic resonance imaging, motor learning, transcranial direct current stimulation, working memory

1 | INTRODUCTION

Interest in the role of the cerebellum in nonmotor cognitive processing has increased over the last 30 years (Buckner, 2013). In addition to cerebellar lesion work (Ilg et al., 2013; Schmahmann & Sherman, 1998; Timmann et al., 2008), imaging work demonstrated posterior cerebellar activation (King et al., 2019; Stoodley et al., 2012a, 2012b) during a number of nonmotor tasks, (Neau et al., 2000; Ravizza & Ivry, 2001; Stoodley et al., 2012a) and closed-loop cerebello-thalamo-cortical circuits involved in cognition (i.e., prefrontal cortex) in humans (Bernard et al., 2016; Buckner et al., 2011; King et al., 2019; Salmi et al., 2010), building off foundational work in nonhuman primates (Dum & Strick, 2003; Kelly & Strick, 2000; Ramnani, 2006). Despite a growing literature demonstrating cerebellar activation during nonmotor cognitive processing, little work has investigated how the cerebellum relates to neocortical processing. Past work suggests the cerebellum might provide the neocortex with processing resources, such that when output from the cerebellum is degraded, performance suffers (Bernard, 2022; Bernard et al., 2020; Bernard & Seidler, 2014; Filip et al., 2019; Schmahmann et al., 2019). That is, when tasks become more automatic, individuals rely more on internal models and cerebellar processing, freeing up

neocortical resources, particularly if tasks become increasingly complicated.

Recent advancements in noninvasive stimulation, such as transcranial direct current stimulation (tDCS) allow us to further explore the role of the cerebellum in cognition. Neocortical tDCS typically increases (anodal) or decreases (cathodal) neural activity in the cerebral cortex using a small amount of electrical current, which in turn can impact behavior (Coffman et al., 2014). Notably, though, the cellular structure of the cerebellum seems to reverse the polarity effect of that seen in the cortex. This is purportedly the result of inhibitory Purkinje cells synapsing on the deep cerebellar nuclei (DCN). Critically, the firing of inhibitory Purkinje cells on the DCN stops the excitatory signal from the DCN to the cerebral cortex (Ghez, 1991; Grimaldi et al., 2016). Optogenetic work in rodents demonstrates that exciting Purkinje cells (i.e., increased inhibitory signal to DCN) in the cerebellum results in decreased excitatory signal to the neocortex. Conversely, cerebellar stimulation inhibits the inhibitory circuit (i.e., decreased inhibitory signal to DCN), resulting in increased excitatory signal to the neocortex (Grimaldi et al., 2014; Prestori et al., 2020). These are analogous to anodal and cathodal stimulation, respectively. As such, cerebellar tDCS is a viable approach to noninvasively modulating cerebellar contributions to neocortical processing, as changes in cerebellar function have downstream impacts on neocortical activation and behavior.

Behavioral effects in the human brain broadly demonstrate that cathodal stimulation to the cerebellum results in task improvement, while anodal stimulation hampers performance (Ballard et al., 2019; Cantarero et al., 2015; Ferrucci et al., 2013; Pope & Miall, 2012; Shah et al., 2013). Despite this, it is not clear what neural processing occurs to give rise to these behavioral effects. That is, does stimulation to the cerebellum impact neocortical processing during task performance? The limited literature combining imaging and tDCS focuses primarily on language function, and has demonstrated increases in both cerebellar and neocortical activation as well as increased connectivity after anodal tDCS (D'Mello et al., 2017; Rice et al., 2021; Turkeltaub et al., 2016), though this has not always been consistent (Macher et al., 2014). Outside of language, right anodal cerebellar stimulation improved behavioral performance and connectivity with both prefrontal and anterior cingulate during a motor execution and mental imagery task (Grami et al., 2021). Finally, during finger tapping, polarity-specific modulation of the dentate nucleus has been reported (Küper et al., 2019). This small but growing, the literature demonstrates that cerebellar stimulation results in activation and connectivity changes. However, impacts on neocortical activation patterns remain unclear and past work has primarily focused on language leaving other cognitive domains unexplored.

Here, we were interested in understanding how the cerebellum interacts with the neocortex to support neocortical processing, as a scaffolding mechanism during both explicit sequence learning and verbal working memory performance. That is, when the cerebellum is functioning properly, it can free up neocortical resources and help maintain task performance (Bernard, 2022). As such, we predicted that downregulation of the cerebellum would result in the need for additional neocortical resources to perform a task. As suggested by previous optogenetic work (Grimaldi et al., 2016; Prestori et al., 2020), we predicted that cathodal stimulation to the right cerebellum would increase excitation of the DCN and in turn the neocortex. Further, we predicted decreased cerebellar signal to the neocortex (due to greater DCN inhibition) following anodal stimulation (Grimaldi et al., 2016). Critically, following anodal stimulation, we predicted that neocortical activation would increase in a compensatory manner (i.e., exaggerated unilateral increase in activation and/or bilateral neocortical activation) in response to degraded cerebellar output following anodal stimulation, supporting a scaffolding role of the cerebellum (Bernard, 2022; Bernard & Seidler, 2014). Further, this would result in performance deficits following anodal stimulation unaccompanied by a compensatory response and performance improvements following cathodal stimulation, or anodal stimulation with a compensatory response. That is, if young adults can recruit compensatory cortical resources after anodal stimulation, performance will be maintained (relative to sham), or even improved.

2 | METHODS

Participants were randomly assigned to one of three tDCS stimulation conditions (anodal, cathodal, or sham) and completed both an explicit motor sequence learning and a Sternberg verbal working-memory task to better understand how the availability of cerebellar processing resources impacted neocortical processing. Stimulation was applied to the right cerebellum.

2.1 | Participants

Seventy-five healthy, young adults participated in this study and were provided monetary compensation for their time. Exclusion criteria included left handedness, history of neurological or mood disorders, skin conditions, and history of concussion. Data was not collected for one participant because the participant did not wish to complete the experiment after providing consent. Thus, 74 right-handed participants (38 female) ages 18–30 ($M = 22.03$ years, $SD = 3.44$) were considered for the final analysis. For the Sternberg data, an additional two participants were not analyzed because task accuracy was below 20% ($n = 1$) and a computer error interrupted data recording ($n = 1$), for a final sample of 72 participants (anodal = 23, cathodal = 25, sham = 24). Three participants were excluded from the sequence learning analysis due to computer errors ($n = 2$) and excessive movement ($n = 1$), for a final sample of 71 participants (anodal = 25, cathodal = 24, sham = 22). All study procedures were approved by the Texas A&M University Institutional Review Board and conducted according to the principles expressed in the Declaration of Helsinki.

2.2 | Procedure

The entire experiment took approximately 2 h to complete. Stimulation was completed and behavioral data were collected within 80 min. Following the completion of the written consent form, participants completed a basic demographic survey, followed by tDCS (see below for details). After stimulation, which was completed outside the scanner, participants completed a computerized Sternberg (Sternberg, 1966) and sequence learning (Kwak et al., 2012) task in the MRI environment while brain imaging data were collected. Tasks were administered in a predetermined random order (for details, see below). Following the experiment, participants completed a survey of sensations related to tDCS (Fertonani et al., 2015). Common sensations such as tingling and itching were reported, though there were no reports of major discomfort.

2.3 | tDCS stimulation parameters

Cathodal, anodal, or sham stimulation was administered using a Soterix 1 × 1 tES system. Human modeling work has shown that cerebellar tDCS maintains current density and spatial distribution remained contained to the cerebellum, despite the hallmark folding found in the cerebellum that causes a particularly complex electric field (Parazzini et al., 2014). Each electrode (5 × 5 cm) was placed in a saline-soaked sponge (6 ml per side), with the stimulation electrode placed 2 cm below and 4 cm lateral of the inion over the right cerebellum, and the return electrode placed on the right deltoid (Ferrucci et al., 2015).

To ensure a proper connection with the scalp, an initial 1.0 mA current was set for 30 s. If contact quality was below 40%, adjustments, such as moving hair to increase the electrode's contact with the scalp, were made and contact quality was rechecked. Following a successful recheck, participants completed a 20-min stimulation session at 2 mA (Ferrucci et al., 2015; Grimaldi et al., 2014, 2016). During the stimulation conditions, maximum stimulation intensity was reached in 30 s and maintained for 20 min, and then would return to 0 mA. During the sham condition, maximum stimulation intensity would be reached, but would then immediately return to 0 mA. There was no additional stimulation during the 20-min session. Participants were blind to the stimulation types. Stimulation was followed by the completion of the behavioral tasks in the scanner.

2.4 | Behavioral tasks

Participants completed an explicit sequence learning task and a working memory task. We chose an explicit sequence learning task, as over the course of learning the neural substrates needed for performance shift from cerebellar to neocortical regions (Doyon et al., 2018). During early learning, several brain regions, including the cerebellum, are active. During this time, internal models are presumably created (Imamizu et al., 2000). As a participant becomes more familiar with the task over time (i.e., learning), cerebellar activation diminishes (Doyon et al., 2018), as there is more of a reliance on the internal models that were created during early learning (Imamizu et al., 2000). The Sternberg task was chosen as it is a classic working memory task (Sternberg, 1966). Past work demonstrates activations in Crus I and Lobule VI during working memory (King et al., 2019; Stoodley, 2012). Past work suggests that when output from the cerebellum is degraded, performance suffers (Bernard, 2022; Bernard et al., 2020; Bernard & Seidler, 2014; Filip et al., 2019; Schmahmann et al., 2019). If cognitive regions within the cerebellum are downregulated, or the communication between these cognitive regions in the cerebellum and the cortex are degraded, then other regions might need to compensate and maintain performance. Therefore, assessing whether there are cortical changes following cerebellar disruption could help explain the necessity of the cerebellum in the cognitive components of motor learning and nonmotor cognitive functioning more broadly.

Task administration started about 20 min after the stimulation session ended and participants took approximately 35 min to complete both tasks (11 min for Sternberg; 14 min for sequence learning; 10 min for instructions and breaks between blocks). This is within the 90 min window in which stimulation is thought to be effective (Nitsche & Paulus, 2001). However, task order was counterbalanced across participants to mitigate the impact of time after stimulation on task performance.

2.4.1 | Sequence learning

The explicit sequence learning task (Kwak et al., 2012) was administered via computer using PsychoPy (Peirce, 2007; Peirce et al., 2019). Participants were shown four empty rectangles and instructed to indicate the location of the rectangle that was filled as quickly as possible via button press using their left middle, left index, right index, and right middle fingers. The stimuli were presented for 200 ms, then the participant had 800 ms to respond before the next stimulus appeared. Each trial lasted 1 s. Random blocks (R) had 18 trials and sequence (S) blocks had 36 trials. Between each block, the letter "R" or the letter "S" was displayed for 20 s to note whether a random or a sequence block was coming, respectively. During sequence trials, participants were told they had to learn a six-element sequence (1-3-2-3-4-2), which was repeated six times within a block. Participants were told that the beginning of the sequence was denoted by a red square to facilitate learning of the sequence. Participants completed three runs which contained two random blocks and three sequence blocks in the following order: R-S-S-S-R. Each run (R-S-S-S-R) took 4 min and 40 s to complete. Participants typically took 30 s or less to begin the next run. For the purposes of analysis here, the first three sequence blocks were considered early learning, the central sequence blocks were middle learning, and the last sequence blocks were considered late learning (Karni et al., 1998). Briefly, early learning is marked by more cognitively focused activities that necessitate active thinking and working memory (Anguera et al., 2012; Doyon et al., 1997; Imamizu et al., 2000). As the skill becomes automatic via

repetition and practice, the late learning phase becomes increasingly motor-focused. Dependent variables used to estimate learning were mean reaction time for correct trials and average total accuracy.

2.4.2 | Sternberg verbal working memory task

The Sternberg Task (Sternberg, 1966) was administered via computer using PsychoPy v3.1.2 (Peirce, 2007; Peirce et al., 2019). At the beginning of a block, participants were given 6 s to remember a string of either one, five, or seven capitalized letters, which represent low, medium, and high load, respectively. After a 1.8-s pause following the presentation of the study letters, participants were shown individual lower-case letters and told to indicate whether the letter was one of the study letters shown at the beginning of the trial, via button press. Each letter was displayed for 1200 ms, separated by a fixation cross that lasted 800 ms.

Each participant completed three runs of this task. Within each run, a participant completed three blocks of 16 trials each, for a total of 144 trials. Within a run, a participant completed each load level once, in a random order. Between each block, there was a prompt that told the participant to prepare for the next block. This lasted 20 s. Participants typically took 30 s or less to begin the next run. Each run lasted 3 min and 38 s. Dependent variables were average reaction time for correct trials and accuracy.

2.4.3 | Behavioral data analysis

Statistical analyses were conducted in R (R Core Team, 2018), using the *lme4* (Bates et al., 2015) package, and *p*-value estimates were determined using the *lmerTest* package (Kuznetsova et al., 2017) via Satterthwaite's degrees of freedom (DF) method. This method estimates the DF denominator, which considers each participant at each level of an IV and the variance gradient of each. This can quickly increase the size of the DF reported. A $p < .05$ threshold was used as the cut-off for significance. When necessary, the *emmeans* package (Lenth et al., 2018) was used to follow-up on significant effects. These comparisons of estimated marginal means used Bonferroni-corrected *p* values.

Task data were analyzed using liner mixed-effects models using restricted maximum likelihood, as it produces unbiased estimates of variance and covariance parameters, ideal for mixed effect models with small samples. Learning phase (early, middle, late) was included as a fixed factor for the sequence task, with all random trials included for comparison. Load (low, medium, and high) was included as a fixed factor for the Sternberg task. Stimulation type (cathodal, anodal, or sham stimulation) was included as a fixed effect and subject was included as a random effect for both tasks. A model was completed for both reaction time for correct trials and accuracy across both tasks. Below is an example of the model used.

$$\text{lmer}(\text{RT} \sim (1 \mid \text{Subject}) + \text{Phase}^{*}\text{Stimulation}, \text{data} = \text{sequence})$$

$$\text{lmer}(\text{RT} \sim (1 \mid \text{Subject}) + \text{Load}^{*}\text{Stimulation}, \text{data} = \text{sternberg})$$

2.5 | fMRI procedures

2.5.1 | Data acquisition

fMRI data were collected at the Texas A&M Translational Imaging Center with a 3-T Siemens Magnetom Verio scanner using a 32-channel head coil. First, a localizer scan was taken (Slice group 1 = sagittal, 5 slices; Slice group 2 = transversal, 10 slices; Slice group 3 = coronal. 6 slices; repetition time [TR] = 8.6 ms; echo time [TE] = 4.00 ms; 1.1 × 1.0 × 7.0 mm voxels; interleaved, slice thickness = 7.0 mm; field of view (FOV) = 250 × 250 mm; flip angle [FA] = 20°; time = 1:25 min) to determine the location of the neural tissue within the scanner. This was followed by 2- and 4-min resting state scans that are not reported here as they were not the focus of this article.

Next, we completed task-based fMRI scans for both the sequence learning and Sternberg task. For the sequence learning task, three scans with alternate phase encoding directions were used to collect blood oxygen level-dependent (BOLD) whole brain scans with a multiband factor of 4 (number of volumes = 134, TR = 2000 ms, TE = 27 ms; FA = 52°, 3.0 × 3.0 × 3.0 mm^3 voxels; 56 slices, interleaved, slice thickness = 3.00 mm, FOV = 300 × 300 mm; time = 4:40 min). For the Sternberg task, three scans with alternate phase encoding directions were used to collect BOLD whole brain scans with a multiband factor of 4 (number of volumes = 103, TR = 2000 ms, TE = 27 ms; FA = 52°, 3.0 × 3.0 × 3.0 mm^3 voxels; 56 slices, interleaved, slice thickness = 3.00 mm, FOV = 300 × 300 mm; time = 3:38 min). An additional high resolution T1-weighted whole-brain anatomical scan was taken (sagittal; GRAPPA with acceleration factor of 2; TR = 2400 ms; TE = 2.07 ms; 0.8 × 0.8 × 0.8 mm^3 voxels; 208 slices, interleaved, slice thickness = 0.8; FOV = 256 × 256 mm; FA = 8°; time = 7:02 min) for data normalization. This was completed after the task-based imaging at the end of the scan session. The above-described scans were all completed well within the 90-min window afforded by 20 min of cerebellar tDCS.

2.5.2 | fMRI data preprocessing and analysis

Images were converted from DICOM format to NIFTI files and organized into a Brain Imaging Data Structure (BIDS) using bidskit (v 2019.8.16; Mike Tyszak, 2016). Functional images were encoded using opposite phase encoding directions. For distortion correction, single 4D images were taken for each participant from each phase encoding direction and were merged. Then fieldmap images were created using FSLs topup to unwrap images (Andersson et al., 2003).

FMRI data was processed using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIBs Software Library, www.fmrib.ox.ac.uk/fsl). Registration to high-resolution structural and/or standard space images was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001). Registration from high-resolution structural to standard space was then further refined using FNIRT nonlinear

registration (Andersson et al., 2007a, 2007b). The following prestatistics processing was applied: motion correction using MCFLIRT (Jenkinson et al., 2002); slice-timing correction using Fourier-space time-series phase-shifting; nonbrain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor. ICA was carried out using MELODIC (Beckmann & Smith, 2004), to investigate the possible presence of unexpected artifacts or activation. Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). Subject-level variables were modeled using fixed effects and group-level comparisons were modeled using FLAME 1 and 2 mixed effects. The subject level contrast contrasted activation conditions between sequence learning phase type [random, (reference), early middle, and late] and working memory loads [low (reference), medium, high]. Group-level analyses contrasted between stimulation condition (cathodal, anodal, sham) and were thresholded nonparametrically using clusters determined by $z > 3.1$ and a (corrected) cluster significance threshold of $p = .05$ (Worsley, 2001). For display purposes, neocortical volumetric maps were projected on the HCP 1200 Subject Group Average Pial Surface (Van Essen et al., 2017) using the Connectome Workbench v. 1.5.0 (https://www.humanconnectome.org/software/get-connectomeworkbench). The two-dimensional cerebellar slices were created using MRICron (https://www.nitrc.org/projects/mricron) on the ch2bet template (Rorden & Brett, 2000). Radiological view was not used.

2.5.3 | Region of interest and behavior analysis

Group differences in percent signal change were also investigated to determine if stimulation affected signal in specific ROIs. Here, we used six masks (Figure 1) that covered both left (BA 7, 39, 40) and right (BA 7, 39, 40) parietal cortices, left (BA 8, 9) and right (BA 8, 9, 46) frontal cortices, and left and right crus I using masks from an existing repository of functional ROIs (Shirer et al., 2012). These masks were fed into FSL's Featquery, which calculated percent signal change for each subject within each of the six ROIs for both the sequence learning and Sternberg task. This was calculated for all participants to look at differences across tDCS stimulation conditions. For sequence learning, we calculated signal change during early, middle, and late learning trials within the sequence > random contrasts. For the Sternberg task, we calculated signal change in the high > low and high > medium contrasts and the low, medium, and high loads individually. ANOVAs were conducted in R using the base statistics (R Core Team, 2018) package to analyze the effect of stimulation group (cathodal, anodal, sham), hemisphere (left or right), and Phase/Load described above on mean percent signal change ($3 \times 2 \times 3$ ANOVAs). Below is an example of the model used.

$$\text{aov}(\text{SignalChangeROI} \sim \text{Stimulation}^{*}\text{Hemisphere}^{*}\text{Phase}, \text{data} = \text{sequence})$$

$$\text{aov}(\text{SignalChangeROI} \sim \text{Stimulation}^{*}\text{Hemisphere}^{*}\text{Load}, \text{data} = \text{sternberg}).$$

Pearson correlations and multiple comparison corrections were also run using the psych (Revelle, 2022) package in R for each ROI within the anodal and cathodal stimulation condition to see if performance was related to signal change. For Sequence learning, we looked at correlations between signal change and task performance within the sequence > random contrast collapsed across all blocks. For Sternberg, we looked at correlations between signal change and task performance within the high> low load contrast. Correlations were corrected using a false discovery rate (FDR) correction.

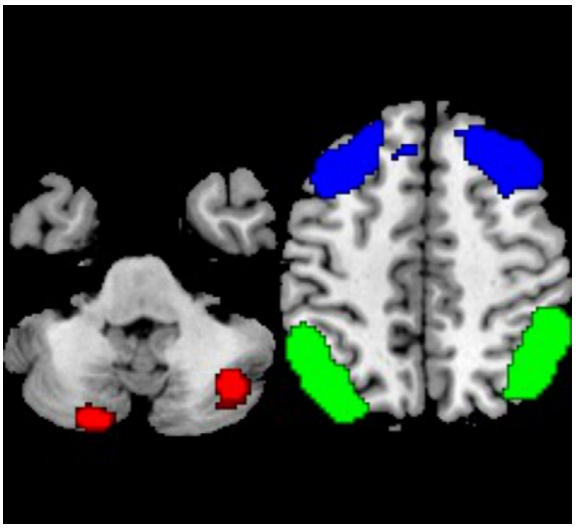

FIGURE 1 Regions of interest are used to examine percent signal change (Shirer et al., 2012). Red = crus I; blue = frontal gyrus; green = parietal gyrus

3 | RESULTS

The main purpose of this study was to understand how the cerebellum interacts with the neocortex during task performance in an explicit sequence learning task and a working memory task following cerebellar tDCS in young adults. We first provide an overview of the behavioral results and imaging for each task domain separately. Then, we will discuss findings from our ROI analyses across both tasks.

3.1 | Sequence learning

3.1.1 | Behavioral results

Mean reaction times (RT) and accuracy for the sequence learning task can be found in Table S1 and in Figure S1. Here we looked to see what effect stimulation (cathodal, anodal, and sham) and learning phase (early, middle, and late) had on both reaction time and accuracy. First, we found a significant phase by stimulation interaction [$F(6, 28{,}332) = 4.96$, $p < .001$], such that the magnitude of change in RT is significantly greater following cathodal stimulation between middle learning and random button presses, compared to anodal and sham.

Additionally, we found a significant effect of learning phase [$F(3, 28{,}332) = 1{,}796.79$, $p < .001$], such that reaction times for early, middle, late, and random learning trials were all significantly different from one another ($ps < .001$). There was no main effect of stimulation [$F(2, 68) = 0.693$, $p = .504$].

When examining accuracy, we found a phase by stimulation interaction [$F(6, 30{,}592) = 3.74$, $p = .001$], such that accuracy was lower during late learning following anodal stimulation, compared to sham ($p = .020$) and cathodal ($p < .002$) stimulation. There was no main effect of stimulation on accuracy [$F(3, 68) = 1.54$, $p = .223$], though we did find an effect of phase [$F(3, 30{,}592) = 16.15$, $p < .001$], such that accuracy was lowest for early learning, and subsequently improved across the other phases. Critically, the outliers seen in late learning in the anodal stimulation condition (Figure S1b) do not affect the interaction. The effect remains whether these data points are included or removed. In sum, cathodal stimulation improved RT during middle learning and anodal stimulation negatively impacted accuracy during later learning phases. More generally, accuracy data also suggest that participants learned across the course of the task.

One issue that might affect behavioral outcomes is task order and stimulation decay, given the time between completion of the tDCS session and the two tasks in the scanner. Even though task order was counterbalanced to mitigate any effect of stimulation decay, the effect of stimulation may still have been lessened during the second task completed in the scanner. We investigated this to quantify the impacts of stimulation on task performance over time. In brief, the impact of task order was minimal, at best, and highly limited, suggesting that stimulation effects persisted over the course of the scanning session. Please refer to the Supplemental Materials (Figure S2) for details.

3.1.2 | Imaging

Patterns of brain activation after stimulation for the three learning phases are presented and described in the Supporting Information. In brief, activation patterns were consistent with canonical findings of cortical motor activation (Dhamala et al., 2003; Seidler et al., 2005), and patterns typically seen during explicit motor sequence learning (Aizenstein et al., 2004; Honda et al., 1998; Yang & Li, 2012) for both sham (Figures S3 and S4 and Table S2) and active (Figures S5 and S6 and Table S3) stimulation groups. Critically, activations were greater in the left supplementary motor area, left precentral gyrus, left lingual gyrus, and the left inferior occipital gyrus during sequence trials, compared to random button press trials. Here, we have focused on patterns of activation by comparing sequence to random blocks after stimulation. Refer to Table 1 for detailed reporting of activation foci and statistics.

3.1.3 | Sequence ≥ random

To investigate the impact of tDCS on brain activation associated with sequence learning we looked at group differences in activation for sequence > random blocks, collapsed across learning phases. When comparing sequence to random blocks (Figure 2a), we found bilateral cortical activation in individuals who received anodal stimulation. Specifically, we saw activations in the left middle frontal gyrus, left the supplemental motor area, left inferior occipital gyrus, left and right inferior parietal, and left and right insula, regions typically active during an explicit motor task (Honda et al., 1998; Yang & Li, 2012). There was also activation in subcortical regions, particularly the thalamus. In the cathodal group (Figure 2b), we found only activations in the left thalamus and left the supplemental motor region during sequence trials compared to random button presses.

We then investigated the activation differences between stimulation groups within the sequence > random contrast (Figure 2c). The anodal stimulation group had greater activation in the left inferior parietal gyrus, left precentral gyrus, and lobules IV–VI in the cerebellum compared to cathodal stimulation. Further, activations in the anodal group were larger in the right middle frontal gyrus and right lobule VI in the cerebellum when compared to the sham group. Only the right caudate nucleus showed greater activation in the cathodal group, compared to the sham group.

We also looked at the effect stimulation had on contrasts between learning phases with the sequence > random contrast (Table 1). First, we examined activation in the early < middle contrast. In the anodal stimulation group, there were larger activations in the right superior frontal gyrus, and the left and right crus I in the cerebellum, compared to cathodal stimulation group. Active stimulation groups showed no regions that were greater than the sham group. However, there were activations that were greater for the sham group compared to cathodal group, perhaps suggesting stimulation tamped down neocortical activations because of more efficient cerebellar processing. Specifically, activations in the left and right hippocampus, left superior frontal gyrus, right putamen, right supplemental motor area, left thalamus, and left crus I were greater for the sham group compared to the cathodal group. Similarly, activations were greater in the right median cingulate gyrus, left precuneus, and left putamen were greater for the sham group compared to anodal.

When we examined the middle > late contrast, we found greater activation in the right median cingulate in the anodal group compared to the sham group (Table 1). Additionally, the anodal group had greater activations in the left thalamus, right caudate, and in the vermis VII, compared to the cathodal group. No activations were significantly greater in the cathodal group compared to sham, though greater right thalamic activation was present in the sham group compared to cathodal.

Together, these results are consistent with our scaffolding hypothesis, wherein there was additional cortical activation in regions relevant to explicit sequence learning (Honda et al., 1998; Yang & Li, 2012) after stimulation (anodal) to the cerebellum that is thought to downregulate its function and output (Bernard et al., 2013; Grimaldi et al., 2016).

3.2 | Sternberg task

3.2.1 | Behavioral results

Mean reaction times and accuracy on the Sternberg task can be found in Table S4 and are depicted visually in Figure S7. Here we looked to

TABLE 1 Significant contrast clusters following stimulation during a sequence learning task

Phase	Stimulation	Region	BA	Voxels	MNI coordinates			Z
					x	*y*	*z*	
Sequence > random	Cathodal	Left thalamus		259	−6	−26	10	4.93
		Left supplementary motor area	Left-BA6	153	0	−6	56	5.26
		Left middle occipital gyrus	Left BA18	136	−20	−102	6	6.67
	Anodal	Left inferior parietal, but supramarginal, and angular gyri	Left-BA40	1987	−40	−40	42	7.13
		Left supplementary motor area	Left-BA6	932	−6	16	44	6.11
		Right inferior parietal, but supramarginal and angular gyri	Right-BA40	819	36	−46	42	6.93
		Left inferior occipital gyrus	Left-BA19	464	−46	−72	−4	6.26
		Right fusiform gyrus	Right-BA37	329	38	−70	−16	5.63
		Left insula	Left-BA13	268	−34	18	6	5.7
		Left thalamus		219	−8	−16	10	5.51
		Right angular gyrus	Right-BA39	189	36	−56	54	5.8
		Right insula	Right-BA13	147	40	18	4	5.09
		Right thalamus		110	10	−18	4	5.12
		Left middle frontal gyrus	Left-BA10	100	−32	46	24	4.84
	Cathodal > sham	Right caudate nucleus		145	8	0	12	5.93
	Anodal > sham	Right middle frontal gyrus	Right-BA10	116	28	50	2	4.83
		Right lobule VI, cerebellum		104	38	−44	−28	4.97
	Anodal > cathodal	Left inferior parietal, but supramarginal and angular gyri	Left-BA40	446	−40	−40	42	5.67
		Right angular gyrus	Right-BA39	326	42	−48	38	5.23
		Right angular gyrus	Right-BA39	193	28	−58	52	4.76
		Left lobule IV and V, cerebellum		154	−20	−40	−30	4.47
		Left precentral gyrus	Left-BA4	122	−60	6	32	5.08
		Right lobule VI, cerebellum		108	32	−46	−26	5.01
Sequence; middle < late	Anodal > sham	Right median cingulate and paracingulate gyri	Right-BA25	133	16	−46	38	5.13
	Anodal > cathodal	Left thalamus		195	−10	−16	20	4.78
		Right caudate nucleus		141	18	−8	22	4.2
		Vermis VII, cerebellum		131	0	−74	−22	4.71
	Sham > cathodal	Right thalamus		130				
Sequence > random; early < middle	Anodal > cathodal	Left crus I, cerebellum		384	−20	−82	−22	5.59
		Right crus I, cerebellum		215	28	−78	−22	5.42
		Right medial frontal gyrus, orbital part	Right-BA9	158	10	36	−10	5.02
	Sham > anodal	Right median cingulate and paracingulate gyri	Right-BA25	190	0	−18	48	4.34
		Left precuneus	Left-BA7	133	−14	−36	70	4.94
		Left lenticular nucleus, putamen		121	−30	−12	10	4.83
	Sham > cathodal	Right lenticular nucleus, putamen		519	24	2	6	5.07
		Right hippocampus	Right-BA35	339	16	−34	2	5.04
		Left superior frontal gyrus, dorsolateral	Left-BA9	307	−18	−4	56	4.97
		Left hippocampus	Left-BA35	297	−34	−30	2	4.88
		Left crus I, cerebellum		241	−22	−82	−24	5.49
		Left lingual gyrus	Left-BA19	229	−10	−90	−12	5.26
		Right supplementary motor area	Right-BA6	169	12	6	62	4.83
		Left thalamus		103	−6	−2	10	4.19

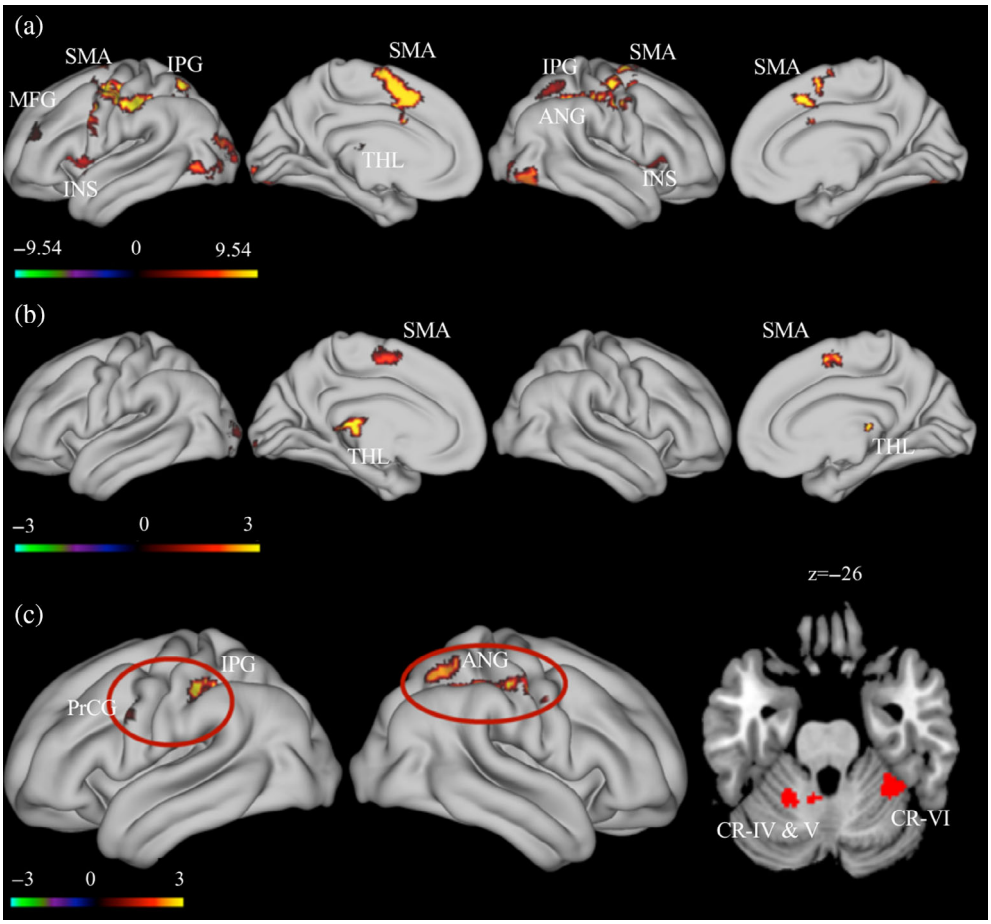

FIGURE 2 Significant activations greater during sequence learning than random trials (sequence>random); (a) anodal stimulation; (b) cathodal stimulation; (c) activations greater following anodal stimulation compared to cathodal stimulation. The color bars display the Gaussianised *t*-values at each region. The maps are thresholded such that only significant results are presented. ANG, angular gyrus; CR IV, lobule IV (cerebellum); CR V, lobule V (cerebellum); CR VI, lobule VI (cerebellum); INS, Insula; IPG, inferior parietal gyrus; MFG, middle frontal gyrus; PrCG, precentral gyrus; SMA, supplemental motor area; THL, thalamus

see what effect stimulation (cathodal, anodal, and sham) and load (low, medium, and high) had on both reaction time and accuracy. When examining the fixed effects of reaction time, there was a significant effect of load [$F(2, 9800) = 665.74$, $p < .001$], such that reaction times for each load condition were significantly different from each other ($ps < .001$). This demonstrates the increase in difficulty associated with increased load. We also found a significant effect of stimulation [$F(2, 68.9) = 4.20$, $p = .011$], such that anodal ($p = .038$) and cathodal ($p = 0.035$) stimulation improved reaction time relative to sham. We did not find a stimulation by load interaction [$F(4, 9800) = 1.05$, $p = .380$].

With respect to accuracy, we only found an effect of load [$F(2, 10{,}290) = 194.93$, $p < .001$], such that accuracy was best on low ($p < 0.001$) load, then medium load ($p < .001$), and then high load ($p < .001$). There was no effect of stimulation [$F(2, 69) = 0.026$, $p = .974$], or a load by stimulation interaction [$F(4, 10{,}290) = 1.29$, $p = .271$]. Like sequence learning, the impact of task order was minimal and highly limited (Figure S8), suggesting that stimulation effects persisted over the course of the scanning session.

3.2.2 | Imaging results

General patterns of activation after stimulation for each load condition are reported in the Supporting Information. Briefly, in the sham stimulation group, we found activation in the frontal and parietal regions one would expect when completing a verbal working memory task (Emch et al., 2019). Contrasts between the load conditions in the sham group (Figures S9 and S10 and Table S5) demonstrated the expected effects of load wherein activation was significantly higher for high relative to low load blocks. We found larger activations during high load than low load, including the left and right inferior frontal gyrus, left middle frontal gyrus, left and right inferior parietal gyrus, and the left supplemental motor area. Additionally, subcortical regions such as the thalamus and right crus I in the cerebellum also showed greater activity when contrasting the high load relative to low load conditions. Unfortunately, contrasts between the active and sham stimulation groups did not reveal any significant differences. This lack of group differences means that all qualitative comparisons of differences are made with caution. Here, we focused on the impact of stimulation when looking at the contrasts between load levels. Activations are reported in Table 2.

3.2.3 | High ≥ low

The anodal group had activations in the right angular gyrus during high-load trials (Figure 3a). Additionally, there were activations in the left superior, left and right inferior, and right middle frontal gyri during high load relative to low in the anodal group. The cathodal group

TABLE 2 Significant contrast clusters following stimulation during a Sternberg task

Load	Stimulation	Region	BA	Voxels	MNI coordinates			Z
					x	*y*	*z*	
High > low	Cathodal	Left thalamus		420	−4	−20	12	6.98
		Right superior frontal gyrus, medial	Right-BA11	339	6	34	46	5.9
		Right insula	Right-BA13	289	38	22	−2	6.71
		Left precentral gyrus	Left-BA4	258	−38	6	50	6.19
		Left inferior frontal gyrus, orbital part	Left-BA47	170	−38	24	−2	6.88
	Anodal	Left superior frontal gyrus, dorsolateral	Left-BA10	2300	−18	62	14	7.37
		Left superior frontal gyrus, medial	Left-BA11	313	−2	28	46	6.05
		Right middle frontal gyrus	Right-BA46	266	38	18	40	5.19
		Right angular gyrus	Right-BA39	204	34	−70	50	7.87
		Right inferior frontal gyrus, triangular part	Right-BA45	198	48	22	4	5.73
		Right inferior frontal gyrus, orbital part	Right-BA47	111	38	44	−4	5.65
High > medium	Cathodal	Left superior frontal gyrus, medial	Right-BA11	380	2	42	44	6.5
		Right crus I, cerebellum		337	32	−66	−36	5.49
		Left middle occipital gyrus	Left-BA19	144	−42	−76	40	4.75
		Right supramarginal gyrus	Right-BA40	135	60	−40	34	5.34
		Left angular gyrus	Left-BA39	111	−44	−56	30	4.89
		Left precentral gyrus	Left-BA4	106	−40	6	42	5.68
	Anodal	Right inferior frontal gyrus, opercular part	Right-BA44	148	44	8	22	5.92
		Left superior frontal gyrus, medial	Left-BA11	134	−10	26	42	4.95
		Left superior frontal gyrus, medial	Left-BA11	133	−4	56	28	5.85
		Right insula	Right-BA13	108	32	18	0	4.28
Medium > low	Anodal	Left insula	Left-BA13	102	−36	20	−2	5.05

(Figure 3b) had activation in left inferior and right superior frontal regions, left precentral gyrus, left thalamus, and right insula. There were no significant activation differences when contrasting active stimulation groups with the sham group.

3.2.4 | High ≥ medium

Individuals in the anodal group (Figure 4a) had activation in frontal regions including the right inferior frontal gyrus, the left superior frontal gyrus, and right insula. Individuals in the anodal group (Figure 4b) had activations in the left superior frontal gyrus, left middle occipital gyrus, supramarginal gyrus, left angular, left precentral gyrus, and right crus I in the cerebellum. Lastly, there were no significant activation differences when contrasting anodal, cathodal, and sham groups.

3.2.5 | Medium ≥ low

Here, the anodal stimulation group showed activation in the left insula under medium load compared to low load. There was no significant activation in the cathodal group. There were no significant activation differences when contrasting anodal or cathodal to sham groups.

Imaging data demonstrated greater frontal (superior, middle, and inferior frontal gyri) and parietal (insula and angular gyrus) activations when processing was high. Further, in the anodal stimulation group, we saw bilateral activation of the frontal gyri (Figure 3a) in line with regions typically thought to be active during a verbal working memory task (Emch et al., 2019).

3.2.6 | ROI analysis

We conducted a ROI analysis to understand whether stimulation modulated mean signal change in crus I, frontal regions, or parietal regions. We also conducted correlation analyses to investigate whether signal change was associated with Sternberg or sequence learning (Figure 6) performance. The detailed statistical results are presented in Table S6. As noted in the methods, all of the analyses here have been corrected for multiple comparisons a false discovery rate (FDR) correction.

3.2.7 | Sequence learning

We examined the effects of stimulation (cathodal, anodal, and sham), hemisphere (left or right), and learning phase (early, middle, and late)

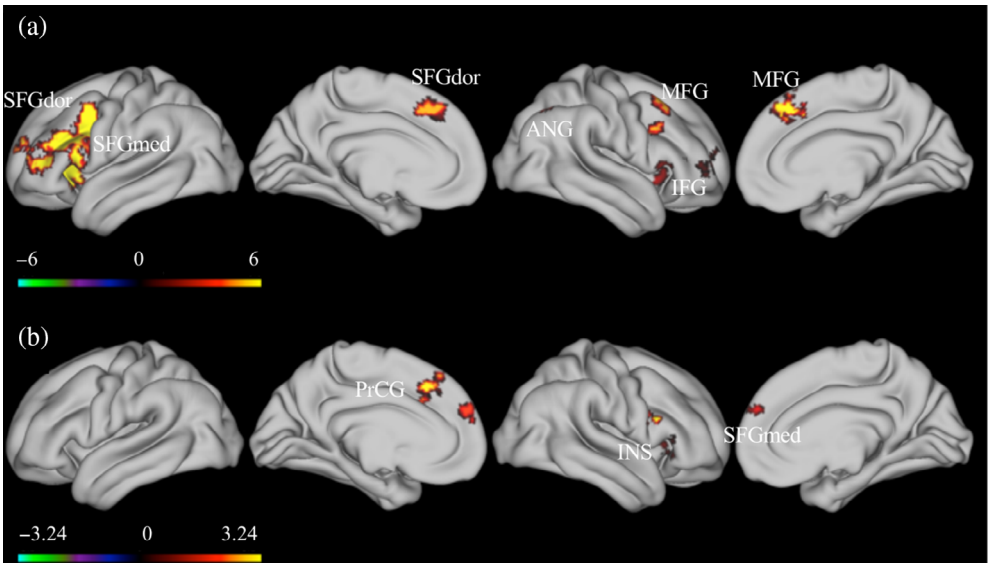

FIGURE 3 Significant contrast activations for the high > low load contrast a Sternberg task; (a) anodal; (b) cathodal. The color bars display the Gaussianised *t*-values at each region. The maps are thresholded such that only significant results are presented. ANG, angular gyrus; IFG, inferior frontal gyrus; INS, insula; MFG, middle frontal gyrus; PrCG, precentral gyrus; SFGdor, superior frontal gyrus, dorsolateral; SFGmed, superior frontal gyrus, medial

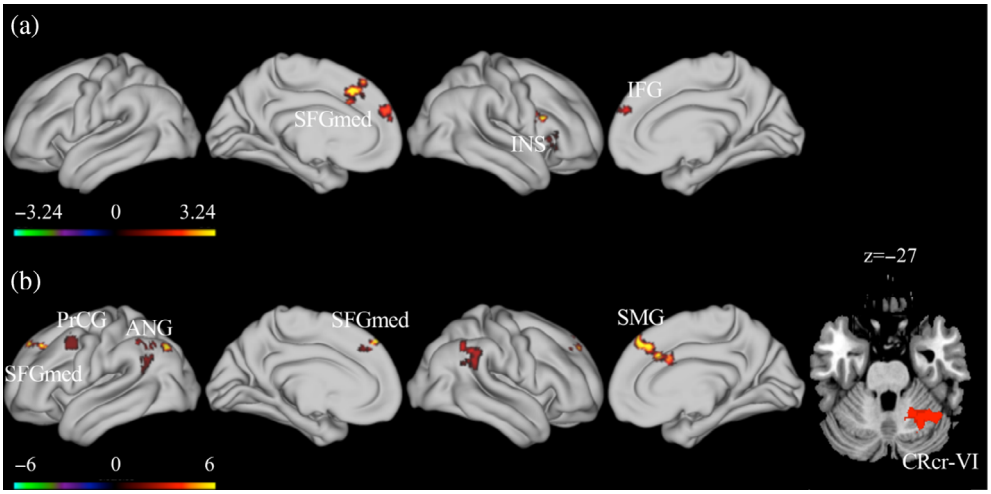

FIGURE 4 Significant contrast activations for the high > medium load contrast a Sternberg task; (a) anodal; (b) cathodal. The color bars display the Gaussianised *t*-values at each region. The maps are thresholded such that only significant results are presented. ANG, angular gyrus; IFG, inferior frontal gyrus; INS, insula; PrCG, precentral gyrus; SFGmed, superior frontal gyrus, medial; SMG, supramarginal gyrus

on signal change within the sequence > random contrast for each ROI (Figure 5). Here, we found a significant Stimulation × Phase interaction on signal change in crus I ($p = .008$; Figure 5a) and the parietal lobe ($p = .037$; Figure 5b) and a trending interaction in the frontal lobe ($p = .073$; Figure 5c). Follow-up analyses suggested signal change was greater in the anodal group compared to cathodal in each region. No other effects reached significance (*ps* > .081).

Correlational analyses (Table S6) did not reveal any significant relationships between signal change and performance when correcting for multiple comparisons.

3.2.8 | Sternberg task

We also examined the impact of stimulation (cathodal, anodal, and sham), hemisphere (left or right), and load (low, medium, and high) on signal change for each ROI. We found a main effect of stimulation ($p = .007$) on mean signal change in the frontal lobes during the Sternberg task (Figure 5d). This was driven by greater signal change in the cathodal and sham group compared to the anodal group. Additionally, we found a main effect of hemisphere ($p = .018$), such that mean signal change was greater in the right parietal lobe, compared to the left parietal lobe when completing the Sternberg task. No other effects reached significance (*ps* > .144). We ran similar analyses examining load contrasts (high > low and high > medium) and no significant effects were found (*ps* > .180).

Correlational analyses suggest that increased signal in left ($r = 0.55$) and right ($r = 0.57$) parietal lobes was associated with increased RT (fdr corrected *ps* < .05), in the anodal group (Figure 6), perhaps demonstrating a failure to compensate for down-regulated cerebellar output, despite taking more time to complete the task. No other associations were significant after correction for multiple comparisons (Table S6).

Cerebellar stimulation seems to impact activation in both cerebellar and neocortical regions. Together, this might provide evidence for our proposed scaffolding effect, such that anodal stimulation might have caused broader neocortical dysfunction instead of a benefit, despite the proposed increase in activation as a compensatory response to degraded cerebellar output.

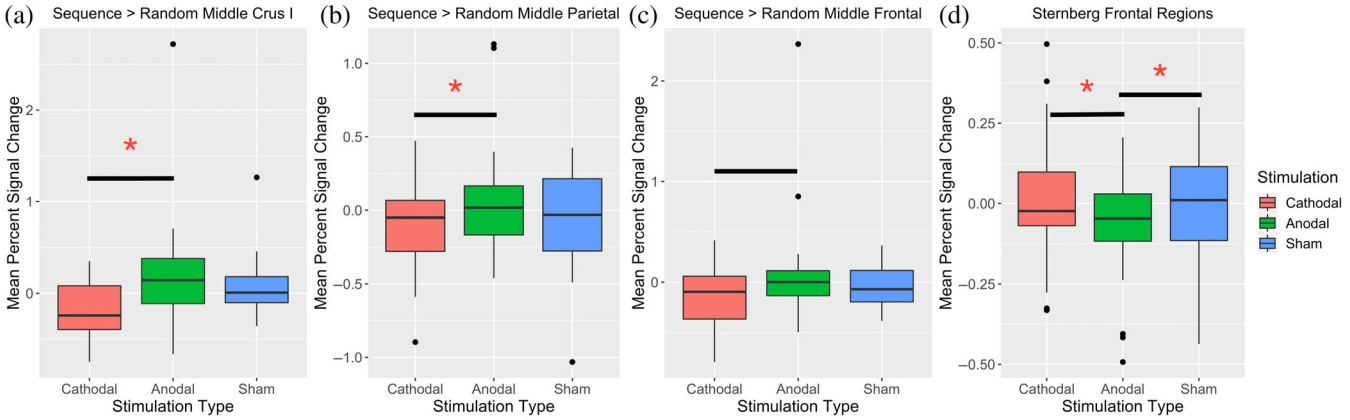

FIGURE 5 Mean percent signal change in sequence > random activations during middle learning by stimulation condition for (a) crus I; (b) parietal ROI; and (c) frontal ROI. (d) Mean percent signal change in frontal ROIs by stimulation condition during the Sternberg task. Dots indicate outliers. Whiskers represent the interquartile range. *indicates significant difference

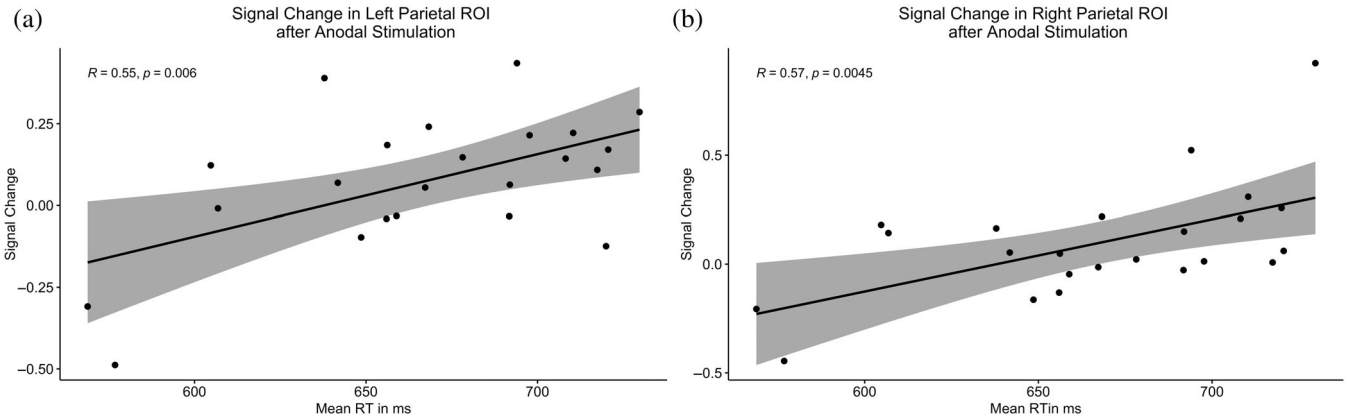

FIGURE 6 Scatter plots displaying correlations between reaction time and signal change in the (a) left and (b) right parietal ROI following anodal stimulation during the Sternberg task

4 | DISCUSSION

The literature implicating the cerebellum in cognitive processing is growing (Buckner, 2013; Schmahmann et al., 2019; Stoodley et al., 2012b), but little work has examined how cerebellar function relates to that in the cerebral cortex during nonmotor tasks. Recent aging work has implicated the cerebellum in cortical scaffolding (Bernard, 2022; Bernard et al., 2020; Bernard & Seidler, 2014; Filip et al., 2019), suggesting that the cerebellum is recruited as a support system for processing through the use of internal models and more automatized processing. Here, we combined tDCS and fMRI to better understand how activation patterns might relate to behavioral performance, and to understand what role the cerebellum might play in cognitive processing, particularly in conjunction with processing in the cerebral cortex. Following either anodal, cathodal, or sham stimulation, participants completed a motor learning (explicit sequence learning) or verbal working memory (Sternberg) task. Broadly, we found increased cortical activation in the anodal stimulation group (thought to downregulate cerebellar function) across task domains, implicating the cerebellum as a critical scaffold for cortical processing (Bernard, 2022; Bernard & Seidler, 2014; Filip et al., 2019), particularly when cerebellar output is thought to be degraded or downregulated. While the impacts of tDCS are not always consistent in the cortex (Imburgio & Orr, 2018), and purportedly have differing polarity-specific effects in the cerebellum (Grimaldi et al., 2016; Prestori et al., 2020), our results show differential effects on cortical activation, and we have replicated effects on sequence learning (Ballard et al., 2019; Ferrucci et al., 2013; Pope & Miall, 2012), supporting the impact and utility of cerebellar tDCS. Together, this work provides novel insights into the potential cerebellar scaffolding mechanism. Results and implications are discussed below.

4.1 | Sequence learning

Consistent with previous findings from our group, we found that the anodal group showed worse accuracy during the late phase of learning (Ballard et al., 2019), and methodological discrepancies with respect

to electrode placement may explain differences from prior work (Ferrucci et al., 2013). In brief, we suggest that anodal stimulation disrupts the formation of internal models during early learning when the cerebellum is particularly active (Ballard et al., 2019; Imamizu et al., 2000), and in late learning when performance would be more automatic, these models cannot be relied upon. Notably, in support of our scaffolding hypothesis, after anodal stimulation, we saw increased frontal and parietal activation in regions related to motor learning and memory, suggesting cortical areas may be compensating for decreased cerebellar output.

Our imaging results demonstrated that anodal stimulation increased cortical activations, in key frontal (Emch et al., 2019; Jonides et al., 1997), parietal (Lissek et al., 2013), and cerebellar (Stoodley et al., 2012a, 2012b) regions associated with nonmotor cognition. Critically, activations in the angular gyrus, supramarginal gyrus, and inferior parietal regions involved with spatial cognition, working memory, and memory retrieval, were greater in the anodal group when compared to cathodal, demonstrating how disruptive anodal stimulation might be in the cortical processing necessary to learn and execute sequenced button responses, resulting in the need for potential compensation (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005; Schneider-Garces et al., 2010). This is made evident by increased motor cortex and middle frontal gyrus activation, regions involved in planning movement (Svoboda & Li, 2018) and orienting attention (Corbetta et al., 1998; Japee et al., 2015) respectively, in the anodal group. The cerebellum may be supporting the spatial processes, memory, and planning (Diedrichsen et al., 2019; King et al., 2019; Stoodley et al., 2012b) needed to complete the sequence learning task; but, anodal stimulation degrades the cerebellar output (i.e., reduces cerebellar output by increasing Purkinje inhibition of deep nuclear cells) necessary to support this process, requiring increased activation in frontal (i.e., precentral gyrus) and parietal regions (i.e., left inferior parietal gyrus) associated with working memory (Lissek et al., 2013). We do want to note that anodal stimulation modulated neocortical activation selectively, depending on whether differences were compared to cathodal or sham stimulation. A direct comparison of signal change within ROIs of the cerebellum, frontal lobe, and parietal lobe demonstrated signal change was greater in the anodal group compared to cathodal during the middle learning phase. No effect emerged in the sham group. This effect between the anodal and cathodal group could suggest that the impairment of anodal stimulation on cerebellar output is far greater than the benefit received from cathodal stimulation, particularly in the parietal and cerebellar regions. Further, the effect of anodal stimulation on the right cerebellum might have broader neocortical effects than cathodal stimulation. That is, despite a compensatory response to degraded cerebellar output, anodal stimulation caused broader dysfunction, as evidenced by poor accuracy in late learning. Together, this provides evidence to suggest that the cerebellum plays a supporting, scaffolding, role in nonmotor cognitive processing, and degradation of cerebellar output has broad functional and behavioral consequences.

Contrary to the current findings, recent work found anodal stimulation improves sequence learning, particularly in middle to late learning phases (Liebrand et al., 2020). We should note however, Liebrand and colleagues showed increases in cortical activation that could be consistent with increased cortical activation because of degraded cerebellar output following anodal tDCS. Therefore, it is possible that anodal stimulation modulated cortical activation similarly to what was found in the current work, but the behavioral outcomes were negated, due to methodological differences (Horvath et al., 2014), such as the online nature of stimulation in the work conducted by Liebrand and colleagues (Liebrand et al., 2020).

Here, we see increased bilateral cortical activation in parietal regions that are typically engaged during sequence learning (Lissek et al., 2013). Though we saw an increase in activation in the anodal group that we argue is compensation for the negative impact on cerebellar processing, the compensation was not enough, resulting in poor performance in late learning. We speculate that internal models were not adequately created during the earlier phases of learning resulting in a greater need for cortical processing; however, this also may explain why accuracy still suffered, as not enough cortical resources were brought on. That is, the internal models stored in the cerebellum needed to make accurate button responses, and used to help support cortical processing, might have been negatively impacted following anodal stimulation, hindering task performance (Bernard & Seidler, 2014; Filip et al., 2019; Ito, 2008). Critically, we see a decrease in accuracy in late learning in the anodal group, which might be a behavioral consequence of degraded cerebellar output, especially when the cortex is not able to fully compensate for the loss of cerebellar resources.

4.2 | Working memory

Behaviorally, we found the expected effect of load, such that performance (both reaction time and accuracy) was best for low load, followed by medium load, and finally worst for high load. We did not find an effect of stimulation on accuracy during performance of the Sternberg task, but we did find that both the anodal and cathodal groups had improved reaction time. Though we predicted performance decrements following anodal stimulation and performance increases following cathodal stimulation, ultimately our results were mixed and limited to reaction time. We acknowledge that reaction time is not the only measure of working memory performance; however, the current data mimic the mixed nature of this literature. Regarding accuracy, there was no effect of stimulation, though accuracy was high, perhaps making it difficult for stimulation to modulate task performance. These ceiling effects might mean that the difficulty across load was not enough to meaningfully change task performance, therefore preventing stimulation from modulating performance based on load.

Activations for both the cathodal and anodal groups were consistent with past work investigating working memory (Emch et al., 2019; Jonides et al., 1997) and could explain the behavioral effect we found on reaction time. Please note, however, that the contrasts between active and sham stimulation were not significant, so our discussion of

activations following anodal and cathodal stimulation alone should be interpreted with caution. Functional patterns in the cathodal group under high load, showed activations in frontal (i.e., middle and inferior orbital frontal gyri), parietal (i.e., angular gyrus) and cerebellar regions (i.e., lobule VIIb) associated with verbal working memory (Jonides et al., 1997), presumably enhancing the ability of these areas (Galea et al., 2009; Grimaldi et al., 2016). However, when contrasting high and low loads in the anodal group, we found greater frontal activations in the inferior and middle frontal gyri, which are also regions implicated in verbal working memory task performance (Emch et al., 2019; Jonides et al., 1997). Critically these regions are involved in cognitive flexibility, planning, inhibition, and abstract reasoning in verbal working memory (Eriksson et al., 2015). Thus, anodal stimulation might be disrupting the ability to inhibit task-irrelevant stimuli, requiring increased processing in frontal regions to support inhibitory mechanisms required for successful working memory processing. We propose that the increased bilateral cortical activation in the current work may be compensation as a result of diminished cerebellar output, given what is known about the impact of anodal stimulation on the cerebellum (Galea et al., 2009; Grimaldi et al., 2016). In the current work, this compensatory response following anodal stimulation might have been effective and helped improve behavioral performance as measured by reaction time. This is in line with previous compensatory models (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005; Schneider-Garces et al., 2010), wherein compensatory responses are effective up to a point. That is, increased activation can effectively help young adults maintain performance, but at higher loads young adults max out their cortical resources and begin to show performance decrements. Because of the load levels used here, we may not have reached a point where young adults were no longer able to compensate for the purported downregulated cerebellar function, as such performance levels remained relatively high throughout the task, and across stimulation conditions. Cathodal stimulation activated expected regions, but also in turn by stimulating cerebellar activity, may have positively influenced performance.

Work by Macher and colleagues applied anodal stimulation to the right cerebellum which resulted in poorer performance on a modified Sternberg task (Macher et al., 2014). Critically, this work also found attenuated signal in the right cerebellum and decreased functional connectivity to the posterior parietal cortex following anodal stimulation. This attenuated signal to the cortex following anodal stimulation is in line with our predictions. In the current work, we found increased signal in the parietal lobes was associated with increased reaction time, perhaps demonstrating a compensatory response, but one that was not great enough to support performance. Thus, it is possible that connectivity to the parietal lobes was also attenuated following anodal stimulation, as might be predicted by Grimaldi et al. (2016), resulting in the need for more cortical processing, but this increase did not ensure successful task completion. Together, if the cerebellum was not processing information from the cortex adequately, more cortical resources would be needed to make up for this, resulting in increased cortical activation.

4.3 | The cerebellum as a scaffolding structure

The current study sought to better understand the role of the cerebellum in cognitive processing. In both a verbal working memory and sequence learning tasks, we found that anodal stimulation resulted in increased bilateral cortical activation in regions previously associated with these tasks (Emch et al., 2019; Jonides et al., 1997; Lissek et al., 2013). Optogenetic work suggests that anodal-like stimulation to the cerebellum will excite inhibitory Purkinje cells, ultimately decreasing signal to the cortex (Grimaldi et al., 2016). Our work here suggests that the cortex may compensate for this lost input and processing from the cerebellum by increasing cortical activation in regions critical for task performance. Specifically, cerebellar internal models are used for greater automaticity on well-learned tasks (Imamizu et al., 2000; Ito, 2008; Ramnani, 2006). However, when cerebellar outputs are degraded, there are negative behavioral implications (Bernard & Seidler, 2014; Filip et al., 2019). This was particularly notable following anodal stimulation when cortical regions are taxed, such as in early learning in the sequence task and high load in the Sternberg task. That is, offloading of processing via internal models may be especially important when tasks get more difficult or require more attention, as the cerebellum may serve as a key scaffolding resource for the cortex (Bernard, 2022). And, when processing is light, this response is not necessary as other mechanisms might be able to efficiently compensate for the loss of cerebellar resources.

Past work in aging (Bernard et al., 2013) and disease (Allen et al., 2007) has suggested that degraded cerebellar output negatively impacts cortical connectivity and activation. Cerebellar resources might be important for cortical processing, as they may provide crucial scaffolding for performance and function (Bernard et al., 2013; Filip et al., 2019). Based on the current work, we suggest that anodal tDCS may mimic this disrupted cerebellar function, ultimately decreasing cerebellar output, which in turn disrupts cortical processing by reducing the inhibitory component in working memory processes and the effectiveness of internal models. This then resulted in the need for increased cortical activation, to maintain task performance. We suggest that anodal stimulation negatively impacts output of the cerebellum via closed-loop circuits with the cortex (Coffman et al., 2011; Kelly & Strick, 2003; Middleton & Strick, 2001), reducing the influence the cerebellum has on cortical processing and in turn, the cortex is no longer able to rely on the cerebellum for support, and must recruit resources elsewhere.

4.4 | Limitations

While our findings provide new insight into the role the cerebellum plays in cognitive processing, there are several limitations. First, comparisons between active and sham stimulation groups during the Sternberg task did not reveal any significant activation differences as it did in the sequence learning data. This could be the result of low task difficulty minimizing the need for more cortical resources as a compensatory mechanism. This limits the extent to which we can

interpret the data. However, we are confident in the effects described above as cortical activation patterns do parallel each other for both the Sternberg and sequence learning tasks. The second limitation is task difficulty, particularly during the Sternberg task. Though the current task seemed to be reasonably difficult in terms of memory load for young adults (Cowan, 2001), accuracy levels across all groups were ~90% or better. Therefore, there was not much room for modulation of task performance. This too may have impacted the cortical findings and lack of group differences when comparing anodal to sham stimulation. This might also explain why there were not significant correlations between signal change and behavior in the sham group.

A third limitation is electrode size. While a large portion of the literature has used the traditional 1 × 1 montage to modulate cerebellar function (Buch et al., 2017; Ferrucci et al., 2015), it is possible that stimulation to the cerebellum was weak, or occurred outside of the right cerebellum due to spread of the signal. However, recent work has found that, following stimulation, stronger e-field distributions and current densities were found in the cerebellum, with less than 4% spread to cortical structures (Parazzini et al., 2014). This provides evidence suggesting that stimulation in humans primarily affected the cerebellum, with little influence on other cortical structures. Further, the current applied is strong enough to cause a functional change in the cerebellum, without causing functional change in surrounding structures. This is supported by behavioral work showing the expected effects of cerebellar stimulation on performance (D'Mello et al., 2017; Küper et al., 2019; Macher et al., 2014; Rice et al., 2021; Turkeltaub et al., 2016). Thus, it is possible the impact of tDCS was not as prominent in the cerebellum or spread to other adjacent cortical regions, inhibiting the effect of stimulation on the cerebellum, though it is unlikely.

5 | CONCLUSION

Here using working memory and explicit motor sequence learning we demonstrated that cerebellar cathodal stimulation resulted in improved performance, and anodal stimulation hindered task performance. This effect of anodal stimulation also resulted in increased cortical activation, which we suggest is a compensatory mechanism due to the purported downregulation of the cerebellum after anodal stimulation. Specifically, when cerebellar output is degraded by anodal stimulation, the scaffolding effect the cerebellum provides is reduced, requiring more cortical activation to compensate for the reduced cerebellar output. This work has a potential to update existing models of aging and disease to include the cerebellum as a structure used to support cognitive processes, which has implications for remediation across clinical diagnoses.

AUTHOR CONTRIBUTIONS

Ted Maldonado and Jessica A. Bernard designed the study. Ted Maldonado collected and processed data. Ted Maldonado and T. Bryan Jackson completed the data analysis and Ted Maldonado and Jessica A. Bernard interpreted the data and drafted the manuscript. T. Bryan Jackson read and commented on the manuscript.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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