Title: Using Real-time fMRI Neurofeedback and Motor Imagery to Enhance Motor Timing and Precision in Cerebellar Ataxia

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JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Motor imagery, especially when used as an adjuvant treatment with physical practice, promises to be a powerful tool for improving function in individuals with movement disorders. Yet, due to its very nature, motor imagery cannot be directly observed. This makes it difficult to assist and evaluate a patient's motor imagery efforts. Brain activity associated with motor imagery is, however, observable through neuroimaging. Moreover, with the recent development of technologies like real-time functional magnetic resonance imaging neurofeedback (rtfMRI-NF), motor imagery "behavior" can be displayed to both the patient and the clinician. ***We hypothesize that if patients could learn to "exercise" their own motor brain networks directly, they could optimize their rehabilitation.*** We seek to examine the feasibility of applying rtfMRI-NF imagery training to individuals with cerebellar ataxia (CA), a movement disorder that results from progressive cerebellar degeneration. Current treatments can slow the rate of motor loss through methods such as physical therapy and core strengthening, but they focus on physical manifestations and do not target the underlying neural mechanisms involved, thereby missing the root cause. In addition to evaluating the feasibility of motor imagery rtfMRI-NF in CA, we will examine the utility of additional at-home therapy, subsequent to the rtfMRI session. Finally, we will use the rtfMRI-NF data for offline analyses for brain mapping, machine learning, and simulating additional rtfMRI approaches to develop future iterations of rtfMRI-NF protocols. This proposal represents the first of its kind in the treatment of CA, with the potential to dramatically improve motor rehabilitation outcomes.

2. Objectives (include all primary and secondary objectives)

Primary Objectives

Aim 1: Use rtfMRI-NF and motor imagery to train CA participants to improve motor accuracy.

- *Aim 1.1:* Train CA participants (N=30) to engage neural regions during motor imagery that are associated with overt finger tapping at slow (1 Hz) and fast (4 Hz) speeds.
- *Aim 1.2:* Correlate motor imagery skill (i.e., slider bar distance from target) with overt tapping performance.

- *Aim 1.3:* Evaluate the relations between overt tapping accuracy and neurological symptoms as well as motor imagery skill with offline assessments of motor imagery ability.

Aim 1 will use rtfMRI-NF during motor imagery to train CA participants to improve motor accuracy. Thirty CA participants will receive NF during motor imagery in an experiment in which we hypothesize that 1) CA participants will be able to control a NF interface; 2) imagery skill will be positively correlated to improvements in overt tapping accuracy; and 3) overt tapping accuracy will correlate with neurological signs, whereas motor imagery skill will correlate with assessed motor imagery ability.

Aim 2: Translate rtfMRI-NF learning into at-home therapy strategies for continued training.

- *Aim 2.1:* Examine whether motor imagery strategies from rtfMRI-NF training translate into successful at-home therapy training
- *Aim 2.2:* Compare motor imagery performance during rtfMRI NF with at-home motor imagery benefits.

Aim 2 will translate rtfMRI-NF learning into at-home therapy strategies for three weeks of continued training in which we hypothesize that 1) continued practice with imagery strategies will lead to additional improvements in motor timing and precision, and 2) performance during rtfMRI-NF training will positively correlate with at-home motor imagery performance.

Exploratory

Aim 3: Design next-generation approaches to rtfMRI-NF. The data from Aim 1 will be analyzed to optimize the future rtfMRI experiments in the CA population. We will examine whether the NF session can be streamlined to deliver more accurate NF in shorter sessions. To enable future studies to operate within an experimental medicine frame work we will examine three major questions. *Aim 3.1* Are there group differences in CA versus healthy controls? *Aim 3.2* Are healthy models of motor imagery viable for CA participant NF? *Aim 3.3* Can the NF session be streamlined to deliver more accurate NF in more efficient sessions?

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Preliminary Data:

We will apply rtfMRI-NF imagery training to people with cerebellar ataxia (CA), a movement disorder that results from progressive cerebellar degeneration. CA individuals experience poor balance, difficulty walking, severe hand tremors, abnormal eye movements, and slurred speech. A key function of the cerebellum is to orchestrate the fine timing and sequencing of motor functions [3]. The cerebellum recognizes spatial and temporal relationships for feedforward predictions [4-7] and then compares the predicted versus actual outcomes and adjusts its output to the cortex [6, 8, 9]. CA signs, therefore, fundamentally reflect a disruption in timing ability. Without a known cure, current treatments include palliative pharmacology and physical, occupational, and speech therapies to strengthen muscles and counteract the symptoms of disease progression [10]. While these treatments can slow the rate of motor loss, they focus on physical manifestations and do not target the underlying neural mechanisms involved, thereby missing the

root cause. Moreover, not all treatments are equally effective for each patient due to the heterogeneity of symptom presentations. We hypothesize that if patients could learn to "exercise" their own motor brain networks directly, they could optimize their rehabilitation.

The National Ataxia Foundation released a report in January 2021 describing the three symptoms that mattered most to those with CA: lack of balance, impaired mobility, and *decreased fine motor skills in the hand*. Uncoordinated hand movements make it difficult to perform activities of daily living, such as writing, typing, eating, drinking, holding a razor or toothbrush, etc. Fine motor skills, therefore, represent an important target for therapeutic intervention and can reasonably be tested in laboratory and MRI settings.

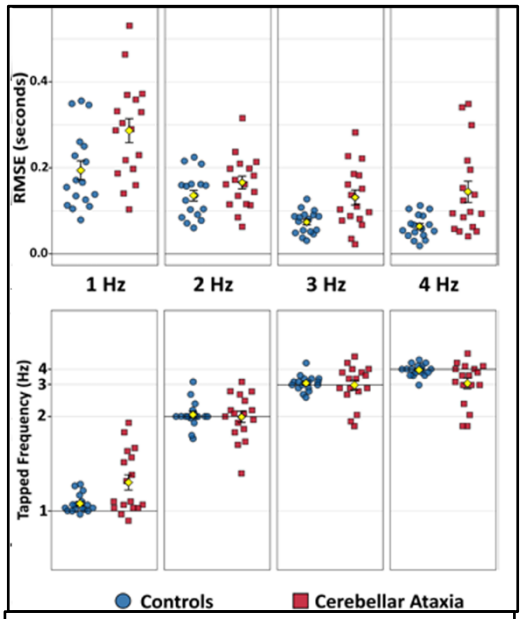

Figure 1. Finger tapping speed and accuracy in CA. Top row: The CA group showed impaired accuracy at 1, 2 (trend), 3, and 4 Hz. Bottom row: The CA group tapped too fast at 1 Hz and too slow at 4 Hz. Yellow= group means. Error bars denote standard error [1].

We compared performance of CA participants (N=17) and healthy controls (N=17) matched for age, sex, and education levels on a task that involved finger tapping in time with a visual cue that flashed at 1, 2, 3, and 4 Hz (Figure 1). Performance feedback was provided as a slider bar that moved to the left as participants tapped too slow and to the right as they tapped too fast. We anticipated that CA participants would be able to use the external cues of the slider bar to correct tapping errors in real time, rather than rely on internal models of timing intervals.

Tapping accuracy, measured by root-mean-squared error (RSME) relative to target, was impaired at all tapping rates. Relative to controls, the CA group's tapping speed was too slow at 4 Hz, and too fast at 1 Hz. Tapping too fast at 1 Hz suggest an inability to control movements to slow down. Over/undershoot corrections in finger movements likely averaged out and masked group differences in speed 2 and 3 Hz, but were revealed in the slow (1 Hz) and fast (4 Hz) conditions. In CA, higher symptom severity, as measured by the International Cooperative Rating Scale (ICARS), was associated with slower tapping and greater error magnitude. Together, these results suggested that accuracy and speed are dissociable measures, with accuracy being the more sensitive measure of motor impairment in CA. Moreover, the 1 and 4 Hz conditions represented especially interesting tapping rates to study given the contrasting behaviors at each speed.

We conducted a follow-up study to explore whether the feedback from the slider bar improved or degraded tapping behavior. We found that both groups slowed their tapping speed in the absence of continuous feedback, but the CA group's tapping accuracy deficits persisted. Based on the differences between 1 and 4 Hz, we speculate that 4 Hz may be close to the tapping limits of CA participants, but 1 Hz represents a trainable target for improving motor timing from paced visual feedback. Thus, this application's focus on 1 and 4 Hz builds on a foundation of preliminary data and aims to tease apart deficits in production from those of top-down feedback processing.
We conducted an fMRI pilot study to identify neural activity patterns associated with right-handed finger tapping in CA participants (N=10) versus matched healthy controls (N=6). The task used in the scanner was the same as that described above. Participants completed 16 total blocks of tapping, with one frequency presented per block, and each frequency (1, 2, 3, or 4 Hz) presented four times. At 1 Hz, the CA group hyperactivated cortical motor regions (e.g., right M1) and hypoactivated anterior cerebellar regions (Lobules V-VI). At 4 Hz, the CA group again hyperactivated cortical motor regions (Figure 2).

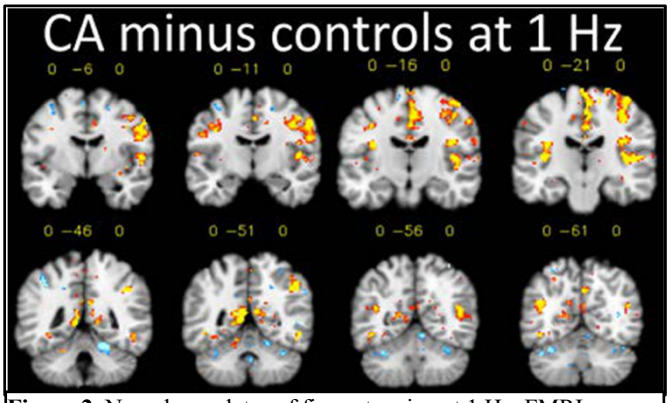

Figure 2. Neural correlates of finger tapping at 1 Hz. FMRI contrasts for tapping at 1 Hz minus rest were compared between groups. Activations in red/yellow = tapping-related in the CA group. Activations in blue = tapping-related in the controls. The CA group hyperactivated cortical motor regions (e.g., right primary motor cortex, M1) and hypoactivated cerebellar regions (lobes V-VI). Activations, p <0.005. Right = right.

Group differences in the cerebellar regions were mitigated by increased cerebellar recruitment in the CA group (relative to 1 Hz). However, instead of recruiting the right anterior cerebellum only (ipsilateral to the finger tapping hand), the CA group recruited the anterior cerebellum bilaterally (Figure 3).

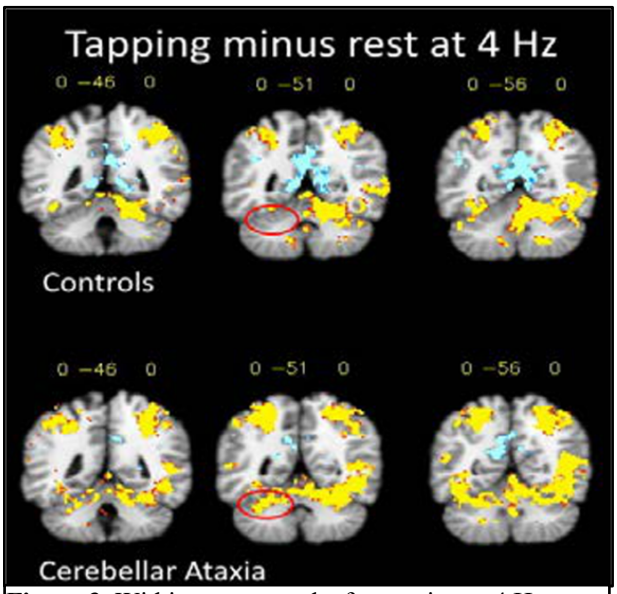

Figure 3. Within-group results for tapping at 4 Hz. FMRI contrasts for tapping at 4 Hz revealed bilateral recruitment of the anterior cerebellum in the CA group that was ipsilateral in controls. Activations in red/yellow = tapping-related. Activations in blue = rest-related. Activations, p <0.001. Right = right.

These results suggest that the CA group recruited cortical motor regions more than controls regardless of speed and performance. The CA group's cerebellar activity was abnormal at both speeds, but showed different patterns of activity. These results demonstrated the feasibility of conducting fMRI research using this task in CA participants, and also pointed to M1 and the cerebellum as potential targets for rtfMRI-NF training.

Motor imagery can be an important rehabilitation tool for people with movement disorders [2]. Loss of motor

function following injury can be regained through neural reorganization, but motor execution is not always possible or safe. Numerous clinical studies have indicated that motor imagery improves motor performance, especially when used as an adjuvant treatment with physical practice [11]. Yet, due to its very nature, motor imagery cannot be directly observed. This makes it difficult to assist and evaluate a patient's motor imagery process. Brain activity associated with motor imagery is, however, observable through neuroimaging. Moreover, with the recent development of technologies like real-time functional magnetic resonance imaging neurofeedback (rtfMRI-NF), motor imagery "behavior" can be displayed to both the patient and the clinician. For example, NF can be presented as a slider bar to indicate the degree to which a motor imagery strategy is working. Moreover, rtfMRI-NF may provide a quantifiable, objective marker of motor imagery performance, since the degree of NF control is proportional to the success of imagery to engage relevant brain regions.

We will combine rtfMRI-NF with imagery to facilitate motor network ("exercise") to improve function in CA. We will use support vector machines (SVMs) to extract motor imagery patterns and perform rtfMRI-NF as pioneered by LaConte [12, 13] (Figure 4). The SVM is first trained on an individual's fMRI patterns while performing a simple motor task (e.g., finger tapping in sync with a flashing visual cue). SVM is then used to provide neurofeedback during a subsequent task (e.g., motor imagery of finger tapping). Information about the brain's activity during motor imagery is relayed back to the person in the form of an "error signal" (i.e., distance from a target on a slider bar). Participants can use this neurofeedback to learn strategies for motor imagery that implicitly steer their brain towards optimal patterns of neural activity. As the participant changes their mental strategy, neurofeedback indicates whether the new strategy is working.

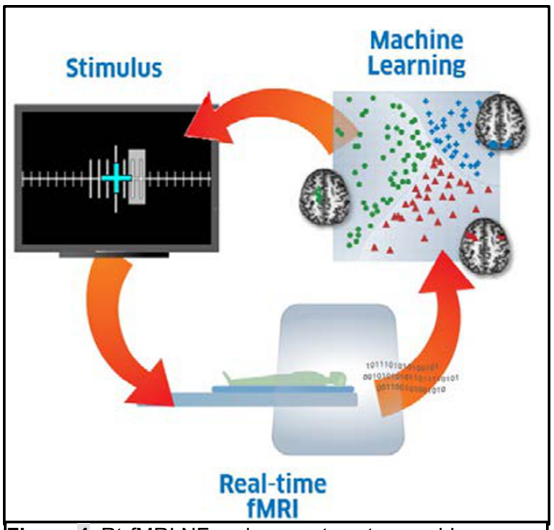

Figure 4. Rt-fMRI NF and support vector machine learning (SVM). *SVM learning*: Inside the MRI, participants finger tap in sync with a flashing crosshair as a slider bar indicates tapping accuracy (right = too fast, left = too slow). FMRI data are preprocessed online and classified via SVM. *RtfMRI-NF*: During motor imagery, a slider bar indicates whether imagery strategies are successfully engaging brain regions as predicted by SVM classifiers. Thus, rtfMRI-NF guides the participant toward engaging motor networks through motor imagery [2].

RtfMRI-NF is safe, can be performed even when physical movement is severely impaired, and targets the underlying neural responses directly rather than the downstream physical signs. Although alternative cheaper and more portable imaging modalities may ultimately be adapted if this line of research garners success, fMRI is currently the best general purpose, whole-brain, non-invasive technology available for human research. Thus, the benefit of rtfMRI is that while this application optimally explores motor imagery's therapeutic potential, it simultaneously addresses a critical need to better delineate motor control and imagery circuitry in CA. Since rtfMRI-NF is a relatively new technology [14], research is only beginning to explore its clinical uses. Most clinical studies to date have been conducted in psychiatric populations [15-26] which have reported symptom reductions in association with NF modulation of brain networks.

Only a handful of rtfMRI-NF studies have been conducted in neurologic conditions. In three stroke studies, participants (N=15 total) were able to modulate brain networks to improve motor and visuomotor function [27-30]. In three studies of Parkinson's disease (PD), [31-33] results have been encouraging. Tinaz et al. (2018) found that eight PD patients were able to modulate connectivity between the insula and prefrontal cortex, which was the *a priori* target of interest; however, the modulation had no effect on motor function. A slightly larger PD study by Subramanian et al. (2016) compared rtfMRI-NF training plus at-home motor training (N=13) to at-home motor training only (N=13). The rtfMRI-NF a priori region of interest was the supplementary motor area (SMA) based on earlier findings that NF training to modulate the SMA correlated with reduction in PD motor symptoms (N=10) [31]. They replicated successful modulation of the SMA using rtfMRI-NF, and motor function improved by 20%. They reported trend-level correlations between NF success and motor function improvements. Moreover, improvements in the rtfMRI-NF group were 2-fold greater than in the exercise-only group (who did not show clinically relevant change), yet this group difference did not reach statistical significance. The authors suggested that studies with larger sample sizes are warranted. It is also notable that PD participants were guided to engage their SMA, even though additional regions were determined to upregulate with NF training, including the frontal lobe, anterior cingulate, basal ganglia, and cerebellum. Thus, our proposed agnostic, whole-brain classifier approach may be advantageous.

In general, due to the novelty of the rtfMRI-NF methodology as applied to clinical populations, methods have varied across studies, and there is still much to learn about how to optimize procedures. Nevertheless, rtfMRI-NF holds great potential as a motor rehabilitation tool. The proposed project will pursue this line of research by using rtfMRI-NF and motor imagery to train CA participants to engage their motor network and improve motor function. We will also test the feasibility of translating this training into at-home therapy. We will use rtfMRI-NF data collected here to develop next-generation approaches to machine learning-based rtfMRI-NF that will inform future protocols.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

To address the objectives listed above, we plan to sample patients with cerebellar ataxia. For participants with cerebellar ataxia, this will be comprised of: 1) a screening phone call, 2) medical record review, 3) one study visit conducted by one of Dr. Marvel's research staff, which will be comprised of both remote, in-person activities, and neuroimaging as detailed below.

The specific study procedures are as follows:

First, a screening phone call will be placed to assess eligibility for participants with cerebellar ataxia. The screening phone call will involve the use of screening scripts to identify if patients are eligible and willing to participate in the research. Furthermore, screening will check for two issues 1) clinical appropriateness and 2) MRI Safety. The only screening test that must be done in-person after consent is obtained is a pre-MRI pregnancy test. Patients with cerebellar ataxia

will also specifically be asked for permission to review their medical records prior to the study visit to confirm eligibility. We will examine patient records in EPIC for additional medical information that may contain relevant study variables.

Next, the first study visit will be coordinated and performed by one of Dr. Marvel's research staff. This will involve a) written informed consent, b) interviewer-administered clinical history questionnaires, c) participant-administered surveys, d) neuropsychological testing, and e) MRI imaging at the Kennedy Krieger Institute.

Teleconsent will be used as opposed to in-person consenting when possible to reduce unnecessary in-person encounters, as described in Section 15, Q1 of the eIRB application. Telemedicine visits will be substituted for portions of in-person visits (e.g., the consent process and the interviewer-administered clinical history questionnaires) when possible. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

Following informed consent, standardized instruments will be administered by a trained interviewer. Completion of these standardized instruments takes approximately 35 minutes.

Standardized Instrument	Approximate Time (minutes)
Hamilton Anxiety Scale (HAM-A)	15
Hamilton Depression Scale (HAM-D)	20

- Anxiety: The Hamilton Anxiety Scale (HAM-A) is a 14-item scale, scored from 0 (not present) to 4 (severe), that measures psychological and somatic symptoms associated with anxiety [34]. A score of less than 17 indicates mild anxiety, 18-24 mild to moderate severity and 25-30 as moderate to severe anxiety.
- Depression: The Hamilton Depression Scale (Ham-D) is a 17-item scale, scored with a 0-3 Likert scale measuring presence and severity of depression [35]. A score of 10-13 indicates mild to moderate depression, and scores greater than 17 as moderate to severe depression.

The following neuropsychological instruments will be administered at the study visit. We may also video the neurological exams (ICARS) for subsequent scoring by the study team. Video recording is especially helpful if there is ambiguity about neurological signs, and we want to get another study team member's consensus rating. The complete battery takes approximately 120 minutes to complete.

Neuropsychological Instrument	Approximate Time (minutes)

Kinesthetic and Visual Imagery Questionnaire (KVIQ-20)	45
Wide Range Achievement Test (WRAT-IV)	30
Cerebellar Cognitive Affective/Schmahmann Syndrome Scale (CCAS-Scale)	15
International Cooperative Ataxia Rating Scale (ICARS)	30

- Visual and Kinesthetic Imagery: The Kinesthetic and Visual Imagery Questionnaire (KVIQ-20), is a 20-item scale that is designed for patients who may have reduced mobility, difficulty standing, or performing certain movements due to neurological complications or disease progression [36]. The questionnaire assesses 10 items for visual imagery rated on a 1 (no image) to 5 (image as clear as seeing) and 10 items for kinesthetic imagery rated on a 1 (no sensation) to 5 (as intense as executing the action) scale.
- Pre-morbid Function: An estimate of pre-morbid intellectual functioning will be measured using the Wide Range Achievement Test – 4th Edition, Reading subtest (WRAT-4) [37]. The WRAT-4 Reading is a standardized test requiring word decoding through letter identification and the ability to read increasingly complex words out of context. Age-referenced standardized scores will be calculated and converted to normalized T scores for analyses. Cognitive decline will be determined comparing neuropsychological test performance to estimated pre-morbid functioning on the WRAT-4 Reading. Specifically, obtaining two or greater standard deviations below the WRAT-4 Reading score on two or more neuropsychological tests will characterize cognitive decline.
- Cognitive Impairment: The cerebellar cognitive affective/Schmahmann syndrome scale (CCAS-Scale), is a screening battery designed to test for disturbances in high functioning domains in patients with cerebellar damage including: executive, visual-spatial, linguistic, and affect regulation [38]. The total possible raw score is 120, with a pass/fail measure where 0 (normal), 1 (possible CCAS), 2, (probable CCAS), and 3 (definite CCAS).
- Ataxia assessment: The International Cooperative Ataxia Rating Scale (ICARS), quantifies neurological impairments rated on an ordinal scale from 0-100. The ICARS assesses 19 items, with 4 subscales: posture and gait disturbance, kinetic function, speech disorder, and oculomotor disorders [39].

When the neuropsychological testing portion of the visit is completed, they will then be trained on a cognitive task that will be administered inside the MRI. If they are a woman of childbearing age, they will be given a urine drug pregnancy test. If the pregnancy test is positive, they will be removed from the study and PHI and any data collected thus far will be destroyed. After training and pregnancy test if needed, they will be escorted to the F.M. Kirby Research Center across the street, which houses the MRI scanner. Participants will be asked to arrive 1 hour before the MRI scan is scheduled to begin. Total time spent in the scanner will be approximately < 1 hour, and

we will reserve 1 full hour to allow time to get in and out of the scanner for this movement disordered population.

Task	Approximate Time (minutes)
Training on cognitive test (outside the scanner beforehand)	10
MPRAGE	6
Overt tapping	12
Motor imagery	12
Overt tapping	12

Participants will perform an overt tapping test as a baseline measure of online task performance. Therapy begins the next day and lasts for 21 days (participants complete at least 5 days per week to accommodate scheduling conflicts). A final measure of overt tapping will be performed the day after therapy ends. Participants will be randomly assigned to one of three training conditions. Group 1, imagery only; Group 2, overt tapping only; and Group 3, imagery plus overt tapping. During imagery, participants will view the task while imagining that they are finger tapping in time with the flashing cursor, using the imagery strategies identified during their rtfMRI-NF session. During overt tapping, participants will finger tap in time with the flashing cue.

Participants will be instructed to find a quiet room with minimal distractions and remain in a comfortable seated position with their hands resting on the keyboard. All tests include blocks of trials in which either 1 or 4 Hz cues are presented. In the baseline and final measures, a session will consist of one 4-minute test comprised of 12 blocks; each frequency will be presented six times. In the 3-week therapy component, a session will consist of two 2-minute tests comprised of six blocks each; each frequency will be presented three times per block. In all sessions, frequency blocks will be pseudorandomized such that the first block will always be the 1 Hz frequency, and the same frequency will be presented in no more than three consecutive blocks. All blocks begin with 5 seconds of rest, followed by 15 seconds of the flashing cue. After completion of their experience for the day (e.g, vividness of imagery, perceived tapping precision, etc.).

	BASELINE MEASURE		**3 WEEKS OF AT-HOME THERAPY CONDITIONS**				**FINAL MEASURE**	
	Overt tapping (4 min)	Daily log (3 min)	Imagery (4 min)	Overt tapping (4 min)	Imagery + overt tapping (2 + 2 min)	Daily log (3 min)	Overt tapping (4 min)	Daily log (3 min)
Group 1 (n=10)	**X**	**X**	**X**			**X**	**X**	**X**
Group 2 (n=10)	**X**	**X**		**X**		**X**	**X**	**X**
Group 3 (n=10)	**X**	**X**			**X**	**X**	**X**	**X**

b. Study duration and number of study visits required of research participants.

Each participant will have 1 in-person study visit (day 1) that will take about 3-4 hours. Days 2-23 of the study will consist of at-home therapy 5x weekly that may take up to 10 minutes to complete. At-home therapy includes a baseline online measure and log (7 minutes), group designated tasks (See table below) and log (7 minutes), and a final online measure and log (7 minutes). The total duration of the study is 2 years of data collection and analyses (allowing up to 3 additional years of data analyses).

General Study Protocol		
Event	**Tasks Completed**	**Duration**
Screening (phone)	Clinical appropriateness	15-20 minutes
Screening (In-person)	Consent*, pre-MRI pregnancy test	25-30 minutes
In-person visit	Task orientation	10-15 minutes
	MRI: Anatomical scan and rtfMRI-NF	1 hour (42 min active MRI)
	Questionnaires*, assessments*, neurological exam, at-home instructions	2 hours
At-home therapy	Baseline online measure & log	7 minutes
	Training according to group assignment: Group 1 = motor imagery only, Group 2 = overt tapping only, Group 3 = motor imagery plus overt tapping (& daily logs)	7 minutes per day for 3 weeks
	Final online measure & log	7 minutes

* When feasible, these tasks will be conducted by phone

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

N/A

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A

e. Justification for inclusion of a placebo or non-treatment group.

N/A

f. Definition of treatment failure or participant removal criteria.

N/A

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

N/A

h. If biological materials are involved, please describe all the experimental procedures and analyses in which they will be used.

N/A

5. Inclusion/Exclusion Criteria

Study population
For the current study, we propose to recruit a total of N=30 adult participants with cerebellar ataxia. Participants with cerebellar ataxia will be recruited through the Johns Hopkins Ataxia Center. Dr. Rosenthal (Co-I and Ataxia Center Director) oversees the Ataxia Center's new patient registry that will provide an additional source of recruitment. The Ataxia Center in 2019, saw 110 new patients and 243 follow-up visits.

Inclusion criteria: 18-100 years of age, at least 8th grade education, right-handedness, clinical diagnosis of progressive, degenerative cerebellar ataxia by a movement disorder specialist (cerebellar ataxia of unknown etiology, and spinocerebellar ataxias with and without genetic confirmation).

Exclusion criteria: History of Axis I psychiatric disorders (including alcohol and drug dependence), severe or unstable medical disorder, non-ataxia related neurological disorders, such as stroke or epilepsy, history of head injury that resulted in a loss of consciousness greater than 5 minutes and/or neurological sequelae, any condition that is contraindicated for the MRI environment (e.g., metal in the body, pacemaker, claustrophobia), or currently pregnant, and clinical diagnosis of multiple system atrophy (MSA, due to the disruption of the central autonomic network) or Friedrich's ataxia (FA, due to extensive involvement of the spinal cord and loss of sensory fibers in the peripheral nerves). MSA and FA differ substantially from other forms of CA and would greatly complicate interpretation of the data. Eligible subjects may be asked to refrain from medications that affect the central nervous system that would also make data difficult to interpret (e.g., sedatives) for an appropriate period of time prior to scanning. Participants will be excluded if they do not have a home computer with internet available to complete the 3-week at-home component of the study protocol.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

N/A

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variable.

1) Overt tapping accuracy improvements will be analyzed by comparing the mean accuracy on overt tapping between baseline and final measures (pre- and post- NF) to compute a delta

measure that will indicate magnitude of accuracy improvement at each frequency (1 and 4 Hz). This will be analyzed using paired t-tests within frequency conditions.

2) At-home overt tapping accuracy improvements will be analyzed by comparing the mean accuracy on overt tapping between baseline and final measures at home (pre- and post- 3-week at-home therapy training) to compute a delta measure that will indicate magnitude of accuracy improvement at each frequency (1 and 4 Hz). This will be analyzed using paired t-tests within frequency conditions. As a follow-up analysis of improvement during the 3-week therapy (for training Groups 2 and 3 who perform daily overt tapping exercises), the mean accuracy of overt tapping at both frequencies will be measured for each session and compared using repeated measures ANOVAs and post-hoc t-tests as appropriate.

b. Secondary outcome variables.

1) The relation between imagery accuracy and tapping accuracy with supplemental assessments of imagery and motor symptoms will be analyzed using non-parametric correlation tests, such as Spearman's rank-order correlation coefficient test, because of the ordinal values in the KVIQ and ICARS assessments. Mean imagery accuracy and tapping accuracy scores from the final MRI assessment will be compared separately to the KVIA an ICARS.

2) The relation between brain activity during imagery NF and overt tapping improvements will be analyzed using Pearson correlations between the mean of region of interest activity (minus rest) during NF training and the RSME delta scores.

3) The influence of ancillary measures on overt tapping and motor imagery accuracy will be analyzed using non-parametric correlation tests (e.g., Spearman's rank) because of the ordinal values in the HAM-A, HAM-D, CCAS, and WRAT assessments. Mean imagery accuracy and tapping accuracy scores from the final MRI assessment will be compared separately to each of the assessments.

c. Statistical plan including sample size justification and interim data analysis.

We plan to enroll 30 participants in this study. The sample size was determined through a power analyses using G*Power 3.1.9.2 software [40]. Because motor imagery, with or without rtfMRI-NF, has never been used as a treatment approach for people with cerebellar ataxia (CA), as proposed here, our power analyses are extrapolated from information we have obtained that in three prior studies that support the premise and feasibility of Aim 1, which is to use rtfMRI-NF and motor imagery to train CA participants to improve motor accuracy.

In our first study, the behavioral RSME deficits exhibited by cerebellar ataxia participants while performing the same overt tapping task as proposed in Aim 1 was quite robust at both 1 Hz and 4 Hz conditions (relative to controls, N=17 per group) [1]. Applying these data to our model revealed that a **sample size of at least 12** participants per group yielded at least 82% power at the .05 level, one-tailed, to reject the null hypothesis of no differences between groups, based on an effect size of at least .79 (large). Although the proposed study will not include healthy

controls, at least 12 CA participants should be sufficient to elicit RSME performance impairments.

In our second study, a functional MRI study of CA participants and healthy controls while performing the same overt tapping task as proposed in Aim 1 revealed several brain regions that differed between groups at the 1 Hz and 4 Hz conditions (N=6 controls, N=10 ataxia): notably, right M1 and right cerebellar lobe V. Contrast values (1 Hz tapping – rest) for these regions were computed, using atlas-based boundaries [41, 42] for CA participants and healthy controls separately and entered into analyses. For the M1 region of interest (ROI), a **sample size of at least 13** participants per group yielded 82% power at the .05 level, two-tailed, to reject the null hypothesis of no difference between groups at the 1 Hz condition, based on an effect size of 1.2 (large). For cerebellar lobe V, a **sample size of at least 9** participants per group yielded 83% power at the .05 level, two-tailed, to reject the null hypothesis of no difference between groups. Similarly, strong between-group differences were revealed at the 4 Hz condition for the M1 ROI. Atlas-based contrast values (4 Hz tapping – rest) for M1 were computed for each group and entered into analyses. A **sample size of at least 8** participants per group yielded 84% power at the .05 level, two-tailed, to reject the null hypothesis of no difference between groups at the 4 Hz condition, based on an effect size of 1.6 (large). However, group differences for cerebellar lobe V, not were significant in our fMRI study at the 4 Hz condition because the CA group was able to recruit this region vigorously in this tapping condition. Given the low number of participants per group in the functional MRI pilot study, additional brain ROIs were identified by trending between-group differences and entered into the model: left premotor cortex and bilateral lobes VIIB. For these ROIs, **a sample size of 19-29** participants per group yielded at least 80% power at the .05 level, two-tailed, to reject the null hypothesis of no group differences, based on an effect size of at least .78 (large). These measures are conservative given that the ROIs were atlas-based rather than task-based (i.e., the ROI boundaries included voxels that did not differ between groups). Thus, a sample size of 29 would be expected to reveal neural activation abnormalities in a number of regions within the cortex and cerebellum in CA participants.

In our third study, rtfMRI-NF was applied to healthy adults (N=17) while performing the overt tapping and imagery tasks proposed in Aim 1. Results revealed that several brain regions engaged during motor imagery positively correlated with RSME improvements: bilateral M1, right premotor cortex and the SMA. Atlas-based contrast values (motor imagery – rest) for these ROIs were computed. Entering into the model the correlation value and standard deviations between the mean contrast values per ROI and mean RSME “delta” revealed that **a sample size of 17 – 22** participants yielded at least 81% power at the .05 level, one-tailed, to reject the null hypothesis of no linear relationship between motor imagery activation and RSME improvements.

Taken together, we propose to enroll N=30 CA participants into this study. This N will be overpowered for some aspects of the study, such as tapping accuracy. However, we are also taking into consideration that the rtfMRI-NF data was based on healthy controls, and we anticipate greater variability in rtfMRI-NF training in the CA participants. Moreover, a sample size of 30 will allow us some room to make additional comparisons with the at-home therapy data (Aim 2) and exploratory MRI data analyses (Aim 3).

Sample size may be underpowered for the some of the proposed comparisons across aims.
The amount of motor imagery necessary to improve overt tapping performance in CA patients is unknown. We modeled our power analysis parameters to target Aim 1. However, we will compare the neuroimaging data with at-home therapy performance variables (Aim 2) and will use the data from Aim 1 to conduct exploratory analyses to improve future protocols (Aim 3). The current sample size may be too small to detect significant results on all comparisons. Nevertheless, we consider the data we collect here to be highly informative for future studies and will serve as pilot data (and power analyses) for future grant applications.

Statistical methods that will be used with respect to each outcome measure:
In general, comparisons between measures with continuous variables (e.g., accuracy) within participants will be conducted using paired-tests, repeated-measures ANOVAs, and post-hoc t-tests as appropriate. Pearson correlations will be run between continuous variables (e.g., motor imagery accuracy and delta scores). Non-parametric tests will be used when assessments that with ordinal values (ICARS, KVIQ, mood, and cognitive ancillary measures) are included.

d. Early stopping rules.
N/A

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Risks/Benefits

The following relevant risk/benefit considerations and potential ethical issues may arise as part of the proposed study. Any adverse events will be promptly reported to the IRB. As this is not an intervention study, participants will be informed as part of the consent process that their medical care will not be affected or altered by their decision to participate in this research. There are no financial risks to the participant.

MRI: Screening of participants will consist of checks for contraindications to MRI scanning. Urine pregnancy testing will be conducted on-site for women of child bearing age. Currently pregnant participants will be excluded. There are no known significant risks for an MRI exam. Subjects, may, however, experience mild discomfort by the noise made by the magnet during the procedure, bothered by feelings of claustrophobia, or anxiety. There is a risk that the subject may become bored or fatigued with cognitive testing while in the scanner.

EMG: The EMG will be utilized to determine whether participants are moving their finger muscles during the imagery condition in the MRI scanner, in which they are not supposed to do so. To apply the surface electrodes on the participant’s arm, skin prepping gel similar to a gentle exfoliating cream will first be applied and rubbed onto the participant's skin in order to remove any dead skin. There is a risk that subjects may not like the feeling of the cream or that their skin will become slightly irritated. The risks of the electrodes are the same as those of applying a band-aid on someone's arm: subjects may be uncomfortable with the adhesive feeling of the electrodes, and the electrodes might feel similar to ripping off a band-aid when taken off.

Incidental findings: Participants may feel anxious due to the outcome of the MRI examination if an abnormality is detected by the neuroradiologist. Female participants of child bearing age may become anxious if a pregnancy test screen is positive.

Behavioral testing: There is a risk that participants may become fatigued or bored while performing these tasks.

Mood and neurological assessments: Participants may feel uncomfortable or anxious while discussing their mood states with the study team. During the neurological exam, CA participants will be asked to stand, walk, and perform other motor functions while sitting, which may create a fall risk or sense of frustration if the participant has difficulty performing the tasks.

Confidentiality:
Despite all precautions, there is a very small risk that identifying information may be revealed. In addition to the study team, the IRB may access personal identifying information during routine monitoring.

b. Steps taken to minimize the risks.

MRI: Participants who report previous experiences of claustrophobia will also be excluded. All participants will be supplied with ear protection during MRI scanning to reduce noise exposure. If at any time the participant becomes fatigued during cognitive testing, they will have the opportunity to take a break or if needed discontinue the scan. To reduce the risk of dizziness and nausea, subjects will be instructed to enter and exit the MRI scanner slowly and to limit movement while in the MRI scanner.

EMG: To minimize the risk of any discomfort or skin irritation from the skin prepping gel, it will be applied carefully and gently to the subject's arm. It will be made sure that the participant is comfortable with the electrodes when they are put on, and care will be taken when they will be removed in order to minimize any discomfort and skin irritation. If the participant becomes uncomfortable during recording, then the electrodes can be removed early. If the participant has highly sensitive skin or would not like to go through with the EMG, then an EMG recording does not have to be obtained.

Incidental findings: All MRI structural scans will be read by a neuroradiologist within two-weeks of acquisition. In the event of an incidental finding, the PI and Co-I (Dr. Liana Rosenthal) will be contacted immediately. Participants will be contacted by the Co-I (or neuroradiologist, as determined by group discussion) to notify them of the findings via telephone. Dr. Rosenthal can then refer the participant for follow-up care. Participants, upon written permission, may have the MRI findings sent to their primary care physician (PCP). Pregnancy test results will be delivered on the day of the MRI scan in person. If positive, study participation will end. If the participant is anxious or distraught from the test results, Dr. Rosenthal will be on hand to assess the need for immediate or follow-up medical care and can refer accordingly.

Behavioral testing: Prior to testing, participants will be reminded that study participation is voluntary and can be stopped at any time. Participants will receive ample opportunities to rest and take breaks as needed between tests.

Mood and neurological assessments: If the participant becomes anxious or upset while discussing mood states, the experimenter will take a break from questioning until the participant is ready to continue. The participant may discontinue at any time. If the participant exhibits signs of extreme duress, or is found to have severe depression or endorse suicidal ideation, we will involve Dr. Rosenthal for consultation on the matter, engage their PCP, and/or escort them to the Emergency Department as appropriate. To minimize risk of falls during the neurological exam, we will have two experimenters present to assist with balance. If the participant or the experimenter decides that standing or walking will be too risky, that component of the neurological exam will be omitted.

Confidentiality:

- Subjects will be notified that they have passed or failed the screening directly in-person or by telephone. In the event of a screen failure, all documents containing the participant's personal health information will be destroyed. All participants will be assigned a code number to protect confidentiality in lieu of participant names. The code key which includes participant names will be kept separate from clinical data obtained such as MRI, neurological scores, and assessments. Names and contact information will be stored in a locked cabinet in Dr. Marvel's laboratory. Research staff that are IRB approved for this study will have access to this cabinet. Data will be stored on a secure REDCap database with password protections that will be accessible to study team members only. Publication of results will include only de-identified data.

Data Collected in the Study :
This research study will include outside collaborators for data analysis; however, this is not a multisite study. The collaborating site, led by Dr. Stephen LaConte at Virginia Tech (VT) Fralin Biomedical Research Institute, will obtain an independent, non-overlapping IRB protocol for this project because of the separate and distinct protocols that will be carried out at each site. Participant recruitment, testing, and all data collection will occur solely at Johns Hopkins.

Defacing MRI data:
All study-related data containing PHI, including structural MRI data, will be securely transferred from the Kirby Center to Johns Hopkins OneDrive. On OneDrive, structural MRI data will be accessed by an IT-supported lab computer in the Psychiatric Neuroimaging Core to complete the defacing using Pydeface software. The software registers structural images to a custom template and uses the template space to remove all facial features from the structural MRI scan. Header editing software is used to identify header fields and remove all data from Dicom header fields containing PHI. Defacing and header stripping is verified using OsiriX MD Dicom viewer software. We will examine the de-faced images to ensure that the facial soft tissue has been removed successfully.

Defaced MRI data will be copied to Enterprise NAS for image processing and analysis.

Data Storage, Access, and Analysis:
Non-MRI related PHI and LDS data will remain on OneDrive and will be accessed via SafeDesktop. Additional LDS information will be stored on a JH IT-managed Network Attached Storage (NAS) via space allocated through the JHU Psychiatric Neuroimaging Core.

Data Sharing with Virginia Tech:
After verification, MRI and related data in the form of a limited data set (LDS), will be shared with non-Hopkins collaborators at VA Tech using a folder on OneDrive that is separate from the folder with PHI. LDS may include the date of birth, age in years or months, and date of MRI scan. Dr. LaConte's server is behind the VA Tech firewall and adheres to high PHI-protected security standards to safeguard data. We will share MRI and MRI-task behavioral data to VA Tech for analysis only. VA Tech may also be consulted during MRI scans to assist with technical errors for the real-time neurofeedback equipment; however, they will not be directly interacting with research subjects or learn their identity.

c. Plan for reporting unanticipated problems or study deviations.

In the event of an adverse event or serious adverse event that requires medical or professional intervention, the neurologist on the project, Dr. Liana Rosenthal, will be available to assess the level of attention required for immediate medical care. This may consist of escort to the ED or referral for follow-up medical care with the participant's primary care physician or specialist. Furthermore, all events will be reported within 24 hours of the investigator becoming aware of the event to the IRB. Other unanticipated problems will be reported to the IRB within 2 weeks after the investigator becomes aware of the problem.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Every effort will be made to keep the information in the study confidential: (1) subjects will be assigned a code number and the code number only will be used to identify the scanning information, cognitive and behavioral information, or the clinical information that will be analyzed; (2) the computers on which the data will be stored are password protected on a secure server behind the Hopkins firewall; (3) written documents concerning the study will be kept in locked cabinets within locked personnel areas; (4) all personnel involved in the study have completed the appropriate HIPAA training and are fully aware of the need for confidentiality.

e. Financial risks to the participants.

These procedures will be performed at no cost to the subjects.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Cerebellar ataxia participants may not directly benefit as a result of study participation. Data collected from this study may provide important future directions to improve protocols that could in turn benefit cerebellar ataxia patients in the future. Motor imagery, guided by rtfMRI-NF, may provide a novel, safe approach to "exercising" the motor circuitry and providing a new

rehabilitation tool for individuals with cerebellar ataxia. Moreover, this methodology may transfer to treatment for other movement disorders.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will be given $100 for completing the study. Participants will be paid by gift card at the end of the study. Participants will be provided a parking voucher at the first visit (East Baltimore campus).

If participants are from out of town, we may be able to provide one night of complimentary hotel lodging at Residence Inn Baltimore at the Johns Hopkins Medical Campus if needed, along with transportation to and from the hotel and our scanning facility if needed. Funds are limited and will be applied as needed but cannot be extended to all participants.
If a participant leaves the study early, or is dropped from the study by the principal investigator for not complying with the procedures listed in this consent form, he or she will only be paid for the parts of the study that he or she has completed. The study will not reimburse for, or replace, a gift card that has been lost, stolen, or expired.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

N/A

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