5-22-2020

# Efficacy of Rhythmic Auditory Stimulation on Ataxia and Functional Dependence Post-Cerebellar Stroke

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# EFFICACY OF RHYTHMIC AUDITORY STIMULATION ON ATAXIA AND FUNCTIONAL DEPENDENCE POST-CEREBELLAR STROKE

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

May 2020

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ABSTRACT

Ataxia, from Greek meaning, "lack of order," is described as irregular movement and discoordination of body, gait, eyes, and speech. Ataxia is associated with cerebellar damage due to stroke and other cerebellar pathologies. Ataxia frequently results in functional impairment. Standard physical and occupational therapies in stroke rehabilitation facilitate motor recovery, especially within 90 days. However, many patients experience movement derangements beyond this time frame. Rhythmic auditory stimulation has been shown to be an effective intervention in chronic motor deficits like those observed after cerebellar stroke. Efficacy among patients with chronic stroke-induced ataxia is unexplored. This randomized control trial seeks to determine the benefit of rhythmic auditory stimulation over standard of care for rehabilitation of cerebellar stroke-induced ataxia. Patient progress will be assessed using validated disability and ataxia scales. It is projected that rhythmic auditory stimulation will improve ataxia and independence among patients with chronic disability post-cerebellar stroke, versus standard rehabilitation.

# CHAPTER 1: INTRODUCTION

## 1.1 Ataxia

Ataxia characteristically causes a disruption of normal movement. Primary features of ataxia include changes in rate, quality, and performance of movement. Secondary characteristics include delayed movement initiation, inability to maintain consistent force, incoordination, dysmetria, and tremor. In a clinical setting, delayed movement initiation can be observed and detected in visuomotor tracking tasks. For example, during an examination, a patient is asked to use their index finger to mirror an examiner's finger as sudden, rapid horizontal arm movements are made in the air. Patients may also exhibit delayed reaction times; depressed motor responses; and, an inability to maintain constant force. These deficits manifest as difficulty with isometric grip force; difficulty handling and lifting objects between fingers; and, impaired fine movements. Dysmetria is typified by undershooting or overshooting of intended limb positions, such as when approaching a target, and often involves misjudgments of distance or scale. When affecting the lower limbs, dysmetria causes under- and overstepping, influencing gait dynamics, balance, and posture. Involuntary rhythmic, oscillatory body movements are referred to as tremor; and, are often exaggerated during goal-directed movements. A heightened sensitivity of this intention-based tremor to movement leads to further deviations in coordination and movement synergy.[1-6]

Motor impairments associated with ataxia are postulated to relate to loss of excitatory cerebellar input to the primary motor cortex in the cerebrum,[7,8] as well as to disruptions of complex pathways involving analysis and prediction of movement.[9,10] In patients with cerebellar stroke, ataxia has been associated with damage to specific vascular areas. Three paired arteries supply the cerebellum: the posterior inferior cerebellar artery (PICA), the anterior inferior cerebellar artery (AICA), and the superior cerebellar artery (SCA).[11] PICA infarction is associated with gait and postural instability, nystagmus, and

vertigo. Damage to the AICA is tied to dysmetria, Horner's syndrome, unilateral hearing loss, and ipsilateral facial paralysis or anesthesia with contralateral hemi-body sensory loss.[12,13] Damage to the SCA is most closely correlated with ataxia in cerebellar stroke patients. Lateralized cerebellar lesions generally produce ipsilateral motor dysfunctions, while diffuse lesions generate more symmetric derangements. Limb ataxia is noted to occur with damage to the cerebellar hemisphere, while isolated truncal and gait ataxia (with relative limb sparing) correlates with insult to the midline vermis.[2] Due to vast heterogeneity in vascular organization between patients, presentations of cerebellar stroke often overlap regardless of implicated vessel, especially in the case of hemorrhagic infarcts.[12]

On review of the literature on cerebellar stroke, some report that the PICA is the most commonly afflicted vascular territory, with estimates on PICA infarction ranging from 49-63%.[12] Damage to the SCA is thought to occur less frequently, with estimates approximating 16-18% of cerebellar stokes.[14-16] Yet, competing research suggests that SCA infarction may be equally or more prevalent than PICA infarct.[17] A minority of patients experience damage to two or more vascular regions. Regardless of affected territory, ataxia is the most commonly reported sign of cerebellar stroke, suggested by some reports to be present in 60 to nearly 100% of patients on presentation.[11,18]

Gait ataxia is frequently observed in patients with cerebellar damage, and is defined by a stumbling walking pattern; irregular foot placement; increased variability in step time and length; widened stance; and, abnormal joint torque.[19,20] Poor truncal motor control in ataxic patients contributes to gait abnormalities and loss of balance,[21] whether cerebellar insult is due to vascular disease or to a hereditary condition. The heightened risk of falls in these patients leads to decreased functional independence and decreased quality of life.[22,23,24]

## 1.2 Cerebellar stroke

Each year, nearly 800,000 people in the United States are affected by stroke.[25] Of these, approximately 2-3% occur in the cerebellum.[12] Though a fraction of the size of the cerebrum, the cerebellum contains nearly 80% of the brain's neurons. It is believed to play a vital role in regulation of muscle tone and motor coordination, timing, and learning.[26] As with a cerebrovascular accident (CVA) in the cerebrum, a stroke in the cerebellum may be ischemic or hemorrhagic, both of which may lead to potentially devastating effects.

Despite the relatively low percentage of total strokes, cerebellar infarcts are associated with a disproportionate amount of morbidity and mortality.[27] Vasogenic edema is a complication in 17-54% of cerebellar stroke patients,[28] potentially causing numerous life-threatening complications such as hydrocephalus; compression of the midbrain and pons; upward herniation of the superior vermis cerebelli through the tentorial notch; or, downward herniation of the cerebellar tonsils through the foramen magnum.[28] Risk of complication is increased by delayed or missed diagnosis.

Presentation of acute cerebellar stroke is often non-specific, with symptoms such as dizziness, headache, nausea, vomiting, vertigo, or unsteady gait.[11] Ataxia, with its characteristically distorted motor patterns, is believed to occur in 40-97% of patients during the acute or subacute period after cerebellar stroke.[11,13,29,30] Additionally, initial diagnostic workup utilizing CT scan is often inadequate for detection of cerebellar infarcts.[16] Magnetic resonance imaging with diffusion weighted imaging (DW-MRI) remains the gold standard[12], but this is rarely the first modality used to evaluate stroke. There may be a failure to recognize stroke symptoms or an inability to obtain a good neurological examination, causing delay or misdiagnosis in over 25% of cases.[16]

Patients with cerebellar stroke who experience complications like hydrocephalus, brainstem compression, or herniation are more likely to undergo surgery and have poor outcomes than patients without such complications.[28,31,32] Those with more complex strokes often have persistent deficits in motor coordination and functional independence.[13,14,17] Gait ataxia is a frequent sign in patients with acute cerebellar stroke.[18] Studies suggest that ataxic gait persists in 20-50% of patients as a long-term functional disability.[13,17,31,33] Patients who survive are often at increased risk of falls and fear of falling.[34] Stroke patients who fall are twice as likely to sustain hip fracture compared to non-stroke patients.[35]

### 1.3 Motor recovery following stroke

Evidence on long-term functional outcomes following cerebellar stroke is scarce, but existing research suggests that many patients continue to suffer chronic motor derangements and functional impairment despite standard rehabilitation.[14,17,28,31,36] It has been observed that motor recovery following cerebral strokes show a plateau in functional gains after a 90-day acute period.[37-40] The persistence of motor dysfunction appears to be more common in strokes with more severe injury at onset, e.g. larger infarcts, hemorrhagic strokes, and those with complications such as edema or herniation.[17,41] Many patients with chronic post-stroke motor impairments suffer reductions in functional independence, which is closely associated with the ability to ambulate independently.[42]

### 1.4 Traditional stroke rehabilitation

There is a certain level of complexity to conducting large scale, rigorous clinical trials evaluating the efficacy of rehabilitation modalities. Aside from identifying an appropriate cohort group amongst a heterogeneous post-stroke population, there are vast differences in capability across rehabilitation interventions and facility protocols.[30,43] Physical therapies vary

in intensity, duration, and type of intervention, as well as degree of specialist involvement. With regards to specific therapeutic interventions for ataxia, investigations have focused on biofeedback; constraint-induced movement therapy; treadmill training; and, other innovations designed to facilitate motor recovery in stroke patients.[44] While many of these modalities appear promising, research has yet to provide evidence from adequately powered randomized control trials to indicate superiority of any novel methodology over another.[45]

The American Heart Association/American Stroke Association (AHA/ASA) guidelines provide traditional physical therapy (PT), occupational therapy (OT), and speech language therapy (SLT) for stroke patients to foster improvement of balance and walking, task-specific functional independence, and communication, respectively. These practices are the standard of care for stroke rehabilitation,[30] and are directed toward improvements in limb weakness, paralysis, and aphasia. Current research has failed to demonstrate efficacy of any one form of physical therapy over another, whether in cerebral or cerebellar stroke.[46]

Research indicates that the time between stroke onset and initiation of rehabilitation is crucial to maximize recovery outcomes. Specifically, distinctions have been made between functional gains made during the acute versus chronic stages of stroke. Rehabilitation within the acute period of time, defined up to 90 days, has shown the greatest amount of functional improvement.[37,38,47] Part of this immediate recovery is attributed to natural internal healing mechanisms, postulated to involve neural reorganization and compensatory input from non-damaged brain areas.[48] Motor improvements are facilitated through the use of rehabilitation techniques including PT, OT, and SLT, based on the clinical needs of the patient.[44] Beyond 90 days, formal PT and OT, as well as home-based aerobic and training programs, have been implemented for patients with persisting deficits.[45] Benefits of continuing interventions are believed to be marginal in comparison to those incurred over the first 90 days.

It is unclear whether recovery differs between cerebral and cerebellar stroke. No separate standard of care exists for rehabilitation based on stroke location. Little definitive conclusion has been drawn regarding prognostic factors other than that greater functional impairment on admission and concurrent hemiparesis are linked to ataxia and poorer functional recovery after the acute period.[15,29] Additionally, SCA-related infarcts and those presenting with altered mental status appear to correlate inversely with functional recovery. The cause of this finding is believed to relate to edema causing brain stem compression and hydrocephalus, and is generally seen when larger territories are impacted by stroke.[15] In the cerebellum, lesion site may substantially influence outcomes for patients with cerebellar stroke, regardless of the dimensions of the impacted territory.[49] And, those with hemorrhagic lesions suffer more functional impairment compared to those with ischemic damage.[15]

### 1.5 Music therapy

Music therapy is an emerging rehabilitative field that has been used to augment recovery in motor pathologies including stroke and degenerative cerebellar disorders.[50,51] Implemented by a board certified music therapist, music therapy is a broad field including techniques such as rhythmic auditory stimulation or cueing (RAS/C), music supported therapy (MST), and patterned sensory enhancement (PSE).[52] The mechanisms by which music therapy works to facilitate motor recovery are thought to involve neuroplasticity, emotional motivational effects, and entrainment of rhythmic auditory cues.[53,54]

The act of playing and making music incorporates inputs from auditory, sensory, and motor areas of the brain, and stimulates neuroplasticity.[53,55] Dynamic relationships between audio and motor regions appear to be enhanced by emotional and motivational relevance of musical stimuli, and engagement of neural reward networks.[53,54] Studies of MST, in which

patients train using the affected limb, have shown enhanced neuroplasticity in recovery for acute and chronic stroke patients.[53,56,57] Audio-motor coupling and enhanced synchronization of brain areas are thought to contribute to motor recovery in patients who undergo RAS training,[58] which uses external rhythmic auditory cues to promote gait recovery.

### 1.6 Music therapy in stroke rehabilitation

To date, music therapy for motor difficulties after stroke has been reported primarily in cerebral stroke with residual hemiparesis.[59-62] Studies on MST are largely focused on recovery of upper extremity function. RAS has been utilized for gait enhancement in patients with acute and chronic abnormalities in gait, posture, and balance.[51,62] In patients with impaired gait patterns after stroke, use of RAS has produced improvements in gait velocity, stride length, and cadence.[60,63,64] Compared to rehabilitative strategies such as treadmill training (TT) or neurodevelopmental (NDT)/Bobath training (a widely-implemented post-stroke physical rehabilitation approach),[65] RAS has produced superior gains in gait parameters.[51,60] Electromyography (EMG) of muscle activation in stroke patients has shown reduced amplitude variability with RAS, suggesting that rhythmic cues promote consistent timing and uniform motor recruitment through central mechanisms of action.[59,62,64]

Use of RAS in gait rehabilitation is thought to facilitate entrainment, the process by which the oscillatory frequency of an external stimulus is adopted by a "weaker" oscillator, producing synchronization of movements with the provided rhythm.[66] In the context of neuropathological processes and motor abnormalities, the weaker oscillator caused by brain injury, becomes entrained to externally cued rhythms of a metronome or music via proprioceptive feedback mechanisms. It has been suggested that the auditory feedback of music therapy acts somewhat like an external pacemaker, providing immediate feedback and

proprioceptive reafference. Through practice and repetition, discrepancy between footfall and auditory rhythm is minimized, eventually promoting a more stable, regular gait.[67]

There is little research on music therapy in cerebellar stroke and associated ataxia. Most of the literature on music therapy and gait focuses on patients with hemispheric stroke. Outcomes addressed in these studies include gait speed and symmetry. These metrics are subject to impairment in ataxia. Improvements in these metrics are promising for extension of RAS to patients with cerebellar stroke.[68] Few studies have explored the use of music therapy in relation to lesion site; yet, a small body of evidence suggests that motor deficits induced by cerebellar lesions are amenable to improvement with RAS.[64]

### 1.7 Music therapy outside of stroke

Music therapy has been explored as an intervention for other motor disorders.[69] A large portion of work on RAS has focused on its use among patients with Parkinson's disease (PD), as well as multiple sclerosis (MS), cerebral palsy (CP), and Huntington's disease (HD).[50,64,70] These disorders manifest similar dysfunctions in gait and movement, and parallel many motor impairments seen in stroke, despite the unique pathological etiologies of deficit.

In patients with PD, changes in motor function include tremor, rigidity, akinesia, bradykinesia, and postural instability.[71] These symptoms are comparable to motor abnormalities seen in HD and MS patients. These patients may experience an inability to ambulate normally due to tremor, spasticity, ataxia, and disequilibrium.[72] Patients with CP share analogous motor impairments involving postural instability and dystonia (abnormal muscular contractures) and joint subluxation.

Patients with motor abnormalities and gait impairment due to these pathologies have benefited from rhythmic auditory cueing to reduce gait variability and improve function.[73-77]

With use of RAS, patients with PD and MS have shown measurable increases in stride length and swing time, which clinically fosters a reduction in falls.[50,75] Freezing of gait, seen in patients with PD, appears amenable to improvement with use of RAS as well.[78] Patients with CP and dysfunctional joint flexion and contractures have experienced amelioration of abnormalities with RAS training.[79,80] Patients with HD have demonstrated improvements in walking speed with RAS.[81]

Due to observed parallels between cerebellar stroke-induced motor abnormalities and those seen in PD, MS, CP, and HD, the use of RAS in cerebellar stroke is promising. It remains unclear whether motor dysfunction and gait impairment in patients with chronic cerebellar stroke is amenable to improvement with RAS. Analyses of gait impairments in patients with PD indicate distinct spatiotemporal irregularities compared to patients with cerebellar ataxia.[82,83] One can speculate whether neuroplasticity offers partial compensation by recruiting healthy cerebellar networks in these patients.[50] It is possible that similar RAS-facilitated therapies will result in comparable improvements in those with cerebellar stroke.

## 1.8 Statement of the problem

Wide gaps exist in the research of long-term outcomes and rehabilitative strategies for patients with chronic cerebellar stroke. Many experience persistent ataxic gait impairments and functional deficits. Little work has assessed therapeutic interventions in this specific group. Available studies fall short of adequately operationalizing ataxia using clinically validated scales. While rehabilitation utilizing PT and OT remains the standard of care for stroke, these therapies are limited in producing motor recovery after an acute period of 90 days, and potential benefits of other approaches remain unexplored or inconclusive. Music therapy has been proposed as a promising rehabilitative approach for individuals with

motor deficits due to stroke. RAS is associated with gait improvement in acute and chronic stroke patients, as well as in patients with neurological disorders such as PD, MS, CP, and HD. The adoption of RAS, and implications and possible benefits for RAS in patients with chronic post-stroke cerebellar ataxia, warrants additional clinical investigation.

### 1.9 Goals and objectives

The proposed study seeks to explore how rhythmic auditory stimulation compares to the standard of care (PT/OT) in outcomes of 1) improvement in ataxia and 2) improvement in functional independence, for patients with chronic ataxia following cerebellar stroke. Subjects will be randomized to interventions, either RAS or standard of care (PT/OT). They will participate in regularly scheduled therapy and undergo rating with the use of the two scales: Scale for the Assessment and Rating of Ataxia (SARA) and Modified Rankin Scale (mRS). Data will be collected over six months. It is anticipated that those who undergo intervention with RAS will demonstrate superior improvements in ataxia and functional independence, compared to those receiving standard of care rehabilitation techniques. Thus, RAS may hold potential as an approach to continued motor rehabilitation during a period of time generally regarded as resistant to improvement in post-cerebellar stroke patients.

### 1.10 Hypothesis

The implementation of RAS therapy over six months for patients with chronic ataxia and functional impairment post-cerebellar stroke, will produce a difference in the proportion of patients who achieve functional independence as measured by the Modified Rankin scale (mRS); and, change in ataxic symptoms as assessed by the Scale for Assessment and Rating of Ataxia (SARA), in comparison to patients who receive standard of care (PT/OT).

## 1.11 Definitions

Acute: definition of the acute period following stroke lacks standardization across studies. For the purpose of this study, the acute period refers to the first 90 days after stroke onset, as it is generally agreed upon that the majority of motor recovery occurs during this time.[37,38]

Chronic: the chronic phase of stroke is defined here as the time beyond 90 days from stroke onset, during which time persistent ataxia and functional deficits have been noted.[13,14,68,84]

Cerebellar stroke: cerebellar stroke is defined as ischemic or hemorrhagic cerebrovascular accident originating from damage to the vascular structures of the cerebellum.[12] Lesions may be embolic, thrombotic, or originating from vascular dissection or small artery disease.[11]

Ataxia: ataxia is a clinical sign characterized by delayed initiation of movement, inability to maintain consistent force, incoordination, dysmetria, and tremor.[1-4] Clinically validated scales for assessment of ataxia include the Scale for the Assessment and Rating of Ataxia (SARA) and International Cooperative Ataxia Rating Scale (ICARS).[68,85]

Rhythmic Auditory Stimulation (RAS): a subcategory of music therapy, RAS is a motor rehabilitation technique requiring participants to walk to the beat of a metronome or rhythmically-enhanced music. Cue frequency may be adjusted according to patient ability.[50,59]

Standard of care: the standard of care for stroke rehabilitation consists of a multimodal approach incorporating physical therapy (PT), occupational therapy (OT), and speech language therapy (SLT).[30] Within this study, which focuses on motor performance and rehabilitation, standard of care includes PT and OT services.

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# CHAPTER 2: LITERATURE REVIEW

## 2.1 Review of Relevant Literature

### 2.1.1 The functional cerebellum

Anatomical organization of cerebellar circuits and their involvement in motor function is complex. We will first outline the role of the cerebellum in movement to facilitate understanding of the chronic motor deficits experienced by patients after cerebellar stroke. To simplify the systems of cerebellar function, two pathways may be observed: the afferent cortico-cerebellar-cortical circuit, and the efferent the dento-rubro-olivary circuit.[86]

The cortico-cerebellar-cortical circuit is comprised of afferent fibers from the frontal lobe, which travel to the cerebellar cortex via the middle cerebellar peduncle. Disruption of afferent signals from the frontal lobe is associated with metabolic depression of the contralateral cerebellar hemisphere.[87,88] Within the circuit, the dentato-rubro-thalamo-cortical tract conducts signals from the cerebellum. In this pathway, originating neurons travel from the dentate nucleus, through the superior cerebellar peduncle to contralateral red nucleus and ventrolateral thalamus, and finally to the motor cortex. Efferent signaling to the primary motor cortex has historically been considered the primary mechanism by which the cerebellum influences movement, but recent work suggests contributions from premotor cortical areas and regions of the basal ganglia.[89] The dento-rubro-olivary circuit, also known as the Guillain-Mollaret triangle, is comprised of efferent fibers from the dentate nucleus, which pass through the superior cerebellar peduncle to synapse on the contralateral red nucleus. Efferent fibers from the red nucleus synapse with the inferior olivary nucleus, which signals through the inferior cerebellar peduncle to synapse on the contralateral cerebellum. The triangle acts as a regulatory feedback loop for motor activity.[86]

In recent years, conceptual theories on the ways in which cerebellar organization modulates movement and coordination have focused on two internal models.[90,91] The first,

the forward model, theorizes that the cerebellum is responsible for the processing of state-dependent movement; that is, the prediction of sensory consequences of movement. These elements of movement include factors such as position or velocity, and calculation of estimations for the next state.[9] The second, inverse model, suggests that the cerebellum is an orchestrator of motor commands and explicit production of state changes, directly influencing motor commands to match desired sensory outcomes.[9,10]

The two models are proposed to work both independently and in tandem.[92] Work by Jueptner et al. (1997) undertook to explore the relative contributions of the cerebellum in processing sensory information versus active participation in movement generation. Using positron emission tomography (PET) to measure regional cerebral blood flow (rCBF), researchers compared local and spatial extents of cerebellar activation during active arm movement, passive arm movement, imagined motion, and actual motion. Measurements of local extent (as determined by % increase in rCBF at a location) and spatial extent (as determined by voxels) were nearly identical between active and passive arm movement ($p > 0.05$), with only 12% more neuronal activity measured during active movement. This suggests a predominant role for the cerebellum in sensory processing. Similarly, imagined movements were associated with increases in rCBF in the neocerebellar hemisphere and vermis of the posterior lobe. This suggests a role for the cerebellum in movement planning.[93]

Motor outputs associated with the cerebellum are postulated to involve sensory integration of timing and coordination.[94] Time-dependent control relies on the accurate assessment of temporal intervals between sensory stimuli. Movement coordination is associated with state-dependent control, using estimates of body position and motion to determine future motion. Research by Diedrichsen and colleagues attempted to delineate between the two mechanisms which are both associated with the production of temporally

precise motor commands. Using functional magnetic resonance imaging (fMRI), they observed that altering the temporal distance between tasks varied the performance of spaced motor tasks such as the movement of a motor arm and an isometric thumb press. Timing of the thumb press was consistent with a time-dependent control hypothesis when the tasks did not overlap ($t_{(5)} = 2.71$; $p = 0.04$). When tasks overlapped, changing the speed of the motor arm produced a timing change in the thumb press, as predicted by a state-dependent control hypothesis ($t_{(5)} > 2.57$; $p < 0.05$). And, fMRI indicated robust cerebellar activation only with state-dependent control, suggesting a role for the cerebellum in estimations of state and organization as it pertains to coordination.[95] Thus, the cerebellum has been associated with error detection and determination of sensory discrepancies between predicted and actual consequences of movement as state-dependent control mechanisms. Blakemore et al. (2001) then used PET to measure rCBF to observe increased cerebellar activation when patients encountered a delay between self-produced hand movement and externally-produced tactile stimulation ($p < 0.05$). Increasing differences in temporal correspondence (between movement and stimulation) correlated to greater cerebellar activation, suggesting increasing inaccuracy of the forward model's sensory prediction.

### 2.1.2 Cerebellar dysfunction

A large body of research conducted to broaden the understanding of the cerebellum is based on case studies using patients with focal cerebellar injuries. In the context of chronic cerebellar stroke, abnormal movement patterns and motor dysfunction have been frequently observed.[96] One of the more familiar of these works was published by Gordon Holmes in 1917. Presenting patients with cerebellar gunshot injuries, he observed unilateral muscle weakness and loss of muscular tone; slowed and irregular movements; loss of coordination;

tremor; and, dysmetria.[97] Cerebellar abnormalities due to various pathologies such as stroke, malignancy, multiple sclerosis, and spinocerebellar ataxias shared similar motor dysfunctions. The irregular limb movements of ataxia permeated to gait instability, incoordination, slurred speech, and nystagmus.[98] While ataxia is frequently observed following cerebellar stroke, few studies have directly addressed the prevalence of ataxia in the chronic phase.

In addition to abnormalities in motor execution, cerebellar damage has been linked with deficits in procedural learning.[99] Doyon et al. (1997) explored the role of the cerebellum by comparing performance of patients with Parkinson's disease (PD), cerebellar damage, and frontal lobe lesions, against healthy controls. Patients with cerebellar damage and those with severe PD were impaired during the late stages of acquisition of a visuomotor sequence and failed to improve with time as compared to healthy controls [$F(2,44) = 9.81$, $p < 0.001$]. The findings suggested that patients with cerebellar damage and PD fail in aspects of learning related to automatization and fine-tuning of movement.[100] Similar findings were reported by Lang et al. (2002), when comparing patients with cerebellar damage to healthy controls in performance of single and dual motor tasks. Echoing conclusions by Doyon et al. in 1997, patients in the cerebellar group performed poorly in comparison to controls ($p < 0.001$) when addressing components of automaticity such as movement completion and error.[101]

Interruption of visuomotor integration in patients with cerebellar damage does not appear to resolve. Work by Gómez-Beldarrain et al. (1998) explored effects of chronic focal cerebellar lesions on procedural motor learning using the serial timed reaction task (SRTT). Findings indicated that at 29 months (± 22 months, range 6-66 months) as a mean time from unilateral cerebellar stroke, patients displayed a lack of procedural learning when using the ipsilesional hand to complete the SRTT versus controls ($p < 0.005$). Results were universal across patients with cerebellar damage, regardless of lesion location or vascular territory.[102]

Boyd and Winstein (2004) additionally observed non-resolving impairments in timing prediction by patients with chronic cerebellar stroke, despite preserved spatial accuracy. Stroke patients were assessed for differences in motor performance across practice sessions and at a retention test. Cerebellar patients and controls demonstrated reduced tracking errors over the practice period, but patients with chronic cerebellar lesions were unable to reduce lag time of tracking across sessions and at retention testing ($p = 0.270$). This suggests persistent temporal impairment, despite preserved accuracy in spatial tracking.[103]

### 2.1.3 Functional impairment and ataxia in chronic cerebellar stroke

The complex interplay between excitatory and inhibitory cerebellar pathways limits understanding of the precise mechanism by which stroke induces ataxia. Yet, chronic motor dysfunction after cerebellar stroke is thought to be tied to persistent disruption of networks between the cerebellum and the primary motor cortex (M1). Such findings were observed by Farias da Guarda et al. (2010), using transcranial magnetic stimulation (TMS) in patients with unilateral chronic cerebellar stroke to induce asymmetrical hemispheric excitation and to decrease short interval intracortical inhibition (SICI) in the contralesional M1, compared to the ipsilesional M1 and healthy controls ($p = 0.048$). Effects were notable for increased motor dexterity associated with decreased SICI ($p = 0.003$).[8] Using cerebellar intermittent theta burst stimulation (iTBS), Bonnì et al. (2014) modulated cortical-cerebellar pathways in patients with cerebellar injury, noting decreased cerebellar brain inhibition ($p = 0.03$) and increased intracortical facilitation ($p < 0.05$) compared to pre-iTBS recordings. Findings were accompanied by significant improvements in the posture and gait subscales of the modified ICARS (mICARS) (Wilcoxon test $p = 0.02$).[104] These observations indicate that ataxia and gait impairments are tied to alterations in cortico-cerebellar pathways.

Despite the prevalence of ataxia in patients presenting with cerebellar stroke, there have been few additional studies in this population. Research on ataxia has focused on observations of motor recovery during the acute phase of stroke, but fails to operationalize data using clinically validated ataxia scales such as the SARA or ICARS. Work by Chua and Kong (1997) explored functional outcomes in patients with brain stem stroke, observing significant improvements after rehabilitation programs, with nearly half of patients deemed "severely ataxic" upon admission and "mildly ataxic" upon discharge ($p < 0.001$).[29]

Similar improvements were seen using the modified ICARS (mICARS) in work by Nickel et al. (2018), which assessed 15 cerebellar stroke patients throughout a 90-day acute recovery period. While noting substantial recovery of ataxia during this time, the study was limited by its inclusion only of patients with ischemic stroke, mostly isolated to the PICA region, with no brainstem involvement, and small lesion sizes[41] (median size reported by Nickel was 3.4 $cm^3$, while lesions >20 $cm^3$ have been noted in other studies).[33] A study by Bultmann et al. (2014) included cerebellar stroke patients with a mean lesion volume over two times that reported by Nickel et al. (2018) and found that patients with cerebellar stroke continued to suffer gait-related ataxic symptoms at 90 days post-stroke. They experienced persistent impairments in total ICARS, ICARS gait subscale, ICARS lower limb subscale ($p = 0.04$, $p = 0.02$, $p = 0.04$), and gait speed ($p = 0.002$).[13]

Regarding functional impairment, studies document residual deficits after a 90-day recovery period. In a multicenter study of nearly 300 cerebellar stroke patients, Tohgi et al. (1993) performed a 5-year review regarding clinical and prognostic factors and documented classified functional outcomes at 3 months post-stroke. The study included patients with infarctions in the SCA (52%), PICA (49%), and AICA (20%) vascular regions, and those with hemorrhagic transformation. Using unspecified assessment tools, most patients (69%)

were classified as independent; 21% as dependent; 4% as bedridden; and, 5% had died. Of those with lesions to single vascular regions, researchers noted lower rates of independence in patients with SCA infarction ($p < 0.005$), as well as those with multiple vessels involved. Prognosis was worse for patients with poorer levels of consciousness on admission. Patients who underwent surgery were nearly split between independent and dependent outcomes.[17]

A number of smaller studies on long-term outcomes of cerebellar stroke have similar findings to those observed by Tohgi and colleagues. Much of this work has used the Modified Rankin Scale (mRS), which classifies patients according to disability and ability to walk and perform activities of daily life, from 0-6 points.[42] A score of 0 indicates perfect health and absence of symptoms. Scores of 1-5 correlate with increasing disability, meaning an ability to carry out dependent and independent activities of daily living, and walk without assistance. A score of 6 is given to patients who have died. [42] Among stroke patients, categorization is often dichotomized, with a score of 0-2 indicative of relatively "good outcome", while scores of 3-5 are used to indicate "poor outcome."[105]

Ng et al. (2015) reviewed 79 cases of patients with hemorrhagic or ischemic cerebellar stroke, and calculated mRS scores at 3 and 6 months. Analysis of prognostic factors found better outcomes with smaller, non-hemorrhagic strokes.[33] Calic et al. (2015) echoed findings on the differential prognostic implications of small ($<2$ cm$^3$) versus large ( $\geq 2$ cm$^3$) cerebellar infarctions, with better outcomes (mRS = 0-2) tied to smaller lesions (OR 3.97, 95% CI 1.41–11.15; $p = 0.01$).[36] Similar results were seen by Juttler et al. (2009) in a study of long-term outcomes of 56 patients treated surgically for space-occupying cerebellar infarction up to 8 years from stroke;[28] Pfefferkorn et al. (2009) in observing outcomes after suboccipital decompressive craniectomy for cerebellar infarction up to 11 years post-stroke;[31] and, Jauss et al. (1999) in analyzing 3-month outcomes after massive cerebellar infarction.

Many interrelated prognostic factors have been suggested to correlate with poor functional outcomes in patients with cerebellar stroke. These include hemorrhage versus ischemia; vascular territory; edema; brain stem involvement; herniation; and, hydrocephalus.

### 2.1.4 The challenge of rehabilitation in chronic stroke

Persistent functional impairments after an acute recovery period aligns with reports of patients with cerebral stroke. Plateaus in recovery after the acute period result in chronic cerebellar impairments, often in gait and functionality. Current research on long-term outcomes tends to focus on lower limb function and gait. Head-to-head comparison of outcomes amongst studies of long-term ataxia and functional impairment lacks standardization, making comparisons limited.

A large scale, prospective evaluation of recovery of walking ability in stroke patients was conducted by Jørgensen and colleagues (1995), with 804 patients with acute stroke undergoing rehabilitation. Jørgensen's team used the Bobath concept (a widely-utilized physiotherapy approach for patients with motor dysfunction in hemiplegic stroke)[106] and the Barthel Index (BI) (a scale delineating independence, assistance-needed, and non-ambulatory states). Of the non-ambulatory patients on admission, 80% reached best walking function within 6 weeks, and 95% reached it within 11 weeks. For patients needing assistance, similar trends were seen, with 80% reaching best function within 3 weeks, and 95% within 5 weeks. Of all patients admitted with impaired ambulation (non-ambulatory or assistance-needed), 33% improved, 33% failed to improve, 1% deteriorated, and 33% died.[38]

A prospective 6-month study of functional recovery in acute stroke patients was implemented by Lee et al. (2015), using regular interventions and re-assessments by physical, occupational, and speech therapists. Outcomes included the Fugl-Meyer Assessment of

sensorimotor function, Functional Ambulation Category (FAC) of walking independence, Trunk Impairment Scale (TIS), Modified Barthel Index (MBI), and Mini-Mental State Examination (MMSE). Improvement in all outcomes occurred between study initiation and 6-month follow-up, with significant interactions between time points and recovery measures ($p < 0.001$). Findings did reflect a plateau in the Fugl-Meyer Assessment, with little improvement between 3 and 6 months ($p \geq 0.05$). Interestingly, FAC and MBI scores (reflecting gait and functional ability) documented improvements up to 6 months. Of note, patients in the study were fewer ($n = 20$ at 6-month follow up) and younger (mean age = 53.3 years) than those of many previously mentioned studies.

A systematic review by Pollock et al. (2014) attempted to delineate between physical rehabilitation approaches in recovery of function and mobility post-stroke. Outcomes such as independence in activities of daily living (ADLs), motor function, balance, gait velocity, and length of stay were assessed. After analysis of nearly 100 studies, pooled results revealed no significant differences between approaches in improving independence in ADLs ($p = 0.71$) or motor function ($p = 0.41$). These findings illustrate an association between chronic, persistent post-stroke effects on motor ($p = 0.05$) and functional ($p = 0.003$) recovery, consistent with other findings on stroke outcomes,[46] irrespective of rehabilitation technique.

### 2.1.5 Music therapy in stroke rehabilitation

Music-based therapies are a promising new approach to stroke rehabilitation, in both the acute and chronic setting. The lack of effective PT and OT for improving chronic ataxia and functional dependence in post-stroke patients has inspired research in alternative treatments like music therapy. Investigations regarding the most effective techniques have identified different forms of music therapy such as music-supported therapy (MST);

patterned sensory enhancement (PSE); and, therapeutic instrument playing (TIMP) for recovery of upper extremity function.[107] Musical intonation therapy (MIT) and musical neglect training (MNT) have been utilized for recovery of speech and language deficits, as well as hemispatial neglect.[108] Rhythmic auditory stimulation (RAS) using metronome beats or music tailored to walking cadence has shown benefits for recovery of functional gait.

Due to the technique's novelty, evidence for RAS in chronic stroke is limited, and existing work has been largely confined to cerebral stroke. Outcomes have included the Timed Get Up and Go test, Berg Balance Scale, and Fugl-Meyer Assessment. Findings from these studies are limited, but specific areas of improvement have been noted. Auditory-motor coupling and entrainment, or the synchronization of rhythmic auditory stimuli with physical motor behaviors, appears to dominate current theoretic models. Rhythmic beats from external auditory sources promote gait synchronization. Temporal differences between movements and cues provide immediate sensory feedback on gait regularity and timing, allowing feed-forward adjustment and more regular, synchronous movements over time.[58,109]

It is unclear whether these proposed mechanisms apply to patients with cerebellar stroke, with the potential to promote similar improvements in chronic motor impairments. A small body of research suggests that patients with cerebellar stroke are likely to benefit from music therapy as seen after cerebral stroke. A review of the neurobiological basis of rhythmic motor entrainment published by Molinari and colleagues (2003) discussed various cerebellar pathologies including stroke and cerebellar atrophy, and their influences on rhythmic and motor capabilities in patients. When asked to detect changes in frequency of a given auditory stimulus, patients with focal lesions (e.g. stroke patients) performed equally to healthy controls, while patients with degenerative cerebellar pathologies were unable to

detect the same changes. Similarly, patients with cerebellar stroke showed a capacity to tap in synchrony with an auditory rhythm, suggesting preserved ability to entrain external stimuli.[110]

A study by Kobinata et al. (2016) explored immediate effects of RAS on gait patterns in 20 stoke patients, as pertained to the site of lesion (cerebellum, pons, medulla, thalamus, putamen, and corona radiata). Following one 20-minute session of RAS, changes in gait parameters were assessed and compared against pre-RAS values. Results revealed significant increases ($p < 0.05$) in velocity and stride length in patients with lesions of the cerebellum, pons, medulla, and thalamus. In patients with lesions of the putamen and corona radiata, no significant improvements were seen.[64] While results of the study suggest potential benefit for this therapy in patients with cerebellar stroke, all participants were fewer than 94 days from stroke onset. Additional study limitations included a lack of a control group for comparison.

A single case study published by Wright et al. (2016) explored the effects of rhythmic auditory cueing in a patient with chronic cerebellar stroke and associated gait variability. The patient, an 81-year old female at 12 months post-PICA infarction, had an ICARS score of 11; abnormal gait; walking fatigue; and, recurrent falls. Cues were given over three gait trials. Data was obtained on gait variation (measured as coefficient of variation, CoV) and joint kinematics (sagittal hip, knee, and ankle angles). Gait improvements were observed, with reduced variability in step time, stance time, and double support time. Decreased variability of joint motion patterns was observed, especially during the stance phase of the gait cycle for hip motion, and swing phase for the knee.[73] Generalization of these findings is not feasible with an $n = 1$. The findings also reflected immediate, but not long-term, therapeutic effects.

Due to a paucity of research on music therapy, it remains unclear whether functional gains are 1) feasible in the chronic phase in this population; and, 2) subject to improvement with use of RAS among patients with cerebellar stroke. Yet, as cerebellar pathways are vital

to motor learning and integrating sensorimotor patterns affecting functional dependence, interventions that may reestablish these pathways, such as RAS, warrant further exploration.

### 2.1.6 Music therapy in other movement disorders

While investigations are needed to evaluate the benefits of RAS in chronic stroke patients and to study the effects on gait beyond the immediate time frame, observations of RAS in patients with other motor disorders have been promising, and suggest that there may be a beneficial application to patients with chronic cerebellar stroke.

Parkinson's Disease

Literature on the use of RAS in Parkinson's disease (PD) is extensive. In PD, the basal ganglia contain key structures that primarily affect sensory and motor learning.[50,111] Like the cerebellum, the basal ganglia are believed to participate in rhythmic motor entrainment and timing through circuits interconnected with the cerebellum and cortical areas.[110] Use of RAS in patients with PD has been associated with improvements in gait parameters similar to those evaluated in patients with chronic deficits relating to stroke.[112,113]

An early study by Thaut et al. (1996) evaluated RAS in gait training for PD patients with gait deficits involving dysfunctions in velocity, stride length, and cadence. Patients were randomized to three conditions: an experimental group undergoing gait training with RAS; a self-paced group undergoing gait training without RAS; and, a control (no-training) group. After a three-week intervention, patients undergoing RAS training exhibited significant improvements in velocity on flat ($p = 0.007$) and inclined ($p = 0.009$) surfaces; cadence ($p = 0.01$); and, stride length ($p = 0.009$). Differences in velocity and cadence were significantly improved compared to the self-paced group (flat: $p = 0.0307$; incline: $p = 0.0347$; cadence: $p = 0.0340$), and no-training group (flat: $p = 0.0001$; incline $p = .0052$).[74]

Work by Hausdorff et al. (2007) assessed gait changes in patients with PD compared to healthy controls, observing changes in gait symmetry and variability using RAS cadences at 100% (baseline) and 110% speeds. Immediate and 15-minute delayed effects induced by RAS were evaluated. At 100% speed, i.e. the pace at which patients comfortably ambulated prior to training, RAS produced significant increases in gait speed, stride length, and swing time, but did not facilitate changes in stride time or swing time variability. In contrast, RAS set at 110% produced significant improvements in stride length and swing time relative to controls ($p = 0.05$, $p = 0.02$), as well as differences in variability outcomes, compared to no-RAS ($p = 0.004$, $p = 0.03$). An assessment of carry-over of effects revealed immediate and 15-minute delay, sustained improvements.[114] Similar findings have been echoed by multiple research studies, continuing support for the benefit of RAS among patients with PD.[70,115]

Given the similarities of motor deficits and the localized entrainment and timing centers in patients with PD and cerebellar stroke, it is reasonable to consider potential parallel benefits in patients with chronic cerebellar stroke. Recruitment of both cerebral and cerebellar networks is likely required for recovery of motor function in both conditions.[50]

Multiple Sclerosis

Patients with multiple sclerosis (MS) are also hypothesized to benefit from RAS. Similar to PD and stroke, gait pathology in MS is linked to motor abnormalities like tremor, spasticity, ataxia, and loss of balance, resulting in slow, asymmetrical, fall-prone gait. In addition to proposed mechanisms underlying cerebellar ataxia, disruptions in sensation and cognition are believed to contribute to proprioceptive impairments in patients with MS.[116,117]

In a three-week trial utilizing metronome-based RAS in MS patients with moderate gait disability, Shahraki et al. (2017) observed changes in step and stride length, cadence, gait speed, and double support time. Like other studies on RAS in gait impairment, researchers

implemented a protocol including cadences at both 100% and 110%. Subjects in the RAS group demonstrated significant improvements in stride length, stride time, cadence, and gait speed ($p < 0.05$) compared to the non-intervention group. Interestingly, groups did not differ in pre- and post-test double support time ($p > 0.05$), included as a measure of balance and fatigue.[75] Improvements seen in MS patients undergoing RAS training were speculated to reflect improved coordination and gait stability. Notably, the study did not include patients at the most severe end of MS-related gait dysfunction,[118] and further work is needed to determine if the observed benefits of RAS in this study might extend to all MS patients.

Therapy with RAS also appears to facilitate motor gains in patients with cerebellar-predominant MS. A pilot study by Baram and Miller (2007) evaluated walking speed and stride length in MS patients with gait disturbances and disease-induced cerebellar ataxia, compared to healthy controls. Outcomes were assessed during active listening, termed "on-line" condition; and, then without RAS approximately 10 minutes later, termed "off-line." Analysis of gait parameters following the study revealed improvements in speed and stride length for patients with MS, during on-line and off-line conditions. As expected, the healthy controls did not show improvement, likely due to unimpaired baseline status, but actually showed a decrease in gait velocity. This decrease was suspected to be related to the burdening effect of wearing the audio-delivery device. Though promising, results of this study were not evaluated for significance, and sample size was small at 14 patients, making it difficult to draw definitive conclusions on the utility of RAS in this population.

Hypotheses regarding the mechanisms by which RAS facilitates gait improvement in patients with MS focus largely upon the reticulospinal tract, which influences muscle action and tone.[119] Auditory cues are believed to facilitate excitability of spinal motor neurons and activation of motor brain areas, enhancing muscle coordination and response. Like other

theories on the use of RAS in motor disorders, however, support for RAS in MS also credits RAS with entrainment of motor rhythms, provision of external cues to guide attention and automatic control, and motivational effects.

Cerebral Palsy

RAS has been used as an approach to rehabilitation for patients with cerebral palsy (CP), a developmental disorder associated with neuromuscular dysfunction. Like other motor disorders, movements in patients with CP can be characterized by postural instability, muscle contractures, dyskinesia, dystonia, ataxia, and joint subluxation. Like stroke, manifestations of CP may be hemiplegic or spastic.[120] Unlike other disorders where RAS has been evaluated, CP is associated with perinatal or early pediatric brain injury. Most patients with CP have no experience of ever having normal gait. Nonetheless, RAS appears effective in enhancing functional motor patterns in patients with CP, even above those benefits induced by standard rehabilitation techniques.

Work by Kim et al. (2011) evaluated RAS in patients with spastic CP, compared to healthy controls. Gait trials with and without RAS were implemented during a single-day intervention period, with outcomes addressing changes in temporospatial and kinematic parameters. Use of RAS ameliorated proximal joint aberrations in CP patients, compared to baseline recordings: pelvic anterior tilt and abnormal hip flexion in were significantly attenuated during RAS gait trials ($p = 0.008$, and $p < 0.05$ respectively). When subdivided by severity of motor impairment, patients with more severe deficits showed significant gains in symmetry of step length when walking with RAS ($p = 0.030$).[79] Despite such promising findings, no significant differences were observed with RAS regarding gait velocity, cadence, step length, step time, single limb stance, double limb stance, or swing phase. Study limitations included a small sample size ($n = 14$) and a lack of follow-up gait assessments.

Subsequent work has shown benefits for RAS in addressing these same outcomes. In 2012, Kim et al. explored RAS versus Bobath/neurodevelopmental (NDT) therapy in patients with spastic CP, over three weeks. Subjects training with RAS had improvements in proximal joint movement, namely pelvic tilt ($p = 0.006$) and hip flexion ($p < 0.05$). They showed significant gains in temporal gait parameters, such as cadence, velocity, stride length, and step length, ($p \leq 0.001$); and decreases in stride time and step time ($p = 0.001$). Patients treated with NDT failed to achieve similar results, and actually had decreased performance in many of these parameters.[76] While NDT was suggested to enhance postural stability in patients with CP, RAS appeared to be superior in enabling functional gait. While this study enrolled more subjects, it remains on the magnitude of a pilot study ($n = 28$), and had a brief follow-up period, which limits generalization to long-term benefits.

Shin and colleagues (2015) conducted a head-to-head comparison on outcomes of RAS over four weeks in patients with hemiplegia due to stroke or CP. Temporospatial parameters (cadence, velocity, step length, stride length, etc.) of the hemiplegic side failed to improve, while asymmetry during swing and stance phases showed significant improvement ($p = 0.006$) with RAS. Only stroke patients experienced significant benefit in kinematic movements such as hip adduction ($p = 0.039$), and distal joint mobility ($p < 0.05$).[80] Limitations to this study included a lack of a control group and a small sample size of $n = 7$ CP patients, and $n = 11$ stroke patients. As such, these results do not indicate if RAS is an effective intervention in either study population. And, there can only be speculation on the mechanism or localization of pathways relating to hemispheric or spastic outcomes of injury.

Huntington's Disease

Exploration of RAS in numerous motor pathologies has generated interest in implementing RAS in patients with Huntington's disease (HD). Despite being a purely

hereditary condition, some neurodegenerative features of HD share similarities with other neurodegenerative conditions such as PD.

Thaut et al. (1999) explored the use of RAS in HD patients, based on the theory that slowed movements in HD are tied to basal ganglia dysfunction, and may be ameliorated with RAS, similarly to patients with PD. Using metronome and music-based cues, researchers implemented gait trials at patients' preferred pace, and with cues set at 10% below, and 10, 15, or 20% above baseline speed. Except for the most disabled patients, most patients were able to increase velocity during metronome-cued trials ($p < 0.05$). Interestingly, music-based cueing failed to elicit the same effect. When short-term effects of RAS were evaluated in a follow-up, un-cued gait trial, patients showed significant retention of gait improvement ($p < 0.05$) after RAS, and greater carry-over in comparison to training without RAS.[77] Despite ability to modulate gait, however, HD patients were unable to synchronize with rhythmic cues, and those with more severe HD experienced greater deviations from synchrony.

Similar findings were reported by Bilney et al. (2005) and Delval et al. (2008). The former analyzed gait during self-paced and metronome-paced gait trials in 30 HD patients compared to controls. Results showed significant perturbations of variability in timing of footstep cadence for HD patients; and, inability to synchronize with cadences, compared to controls ($p < 0.001$, $p < 0.01$).[81] Delval et al. investigated the effects of a metronome beat set at 120% of baseline speed on gait in HD patients, also revealing an inability to synchronize with given cadences. HD patients failed to exhibit increases in gait speed and cadence, in comparison to healthy controls ($p < 0.05$).[121]

Despite an ability to modulate velocity with rhythmic cues, the inability of HD patients to synchronize timing of gait with given cues suggests that patients may be unable to perceive and adjust to regular time intervals. Failure to synchronize with the metronome as a

means to augment or replace deficient internal cueing, may indicate involvement (and derangement) of neural pathways separate from those implicated in other disorders.

## 2.2 Review of relevant methods

### 2.2.1 Study design

The proposed study is a multi-center, parallel, randomized, controlled trial to compare improvement of ataxia and functional status in chronic cerebellar stroke across patients receiving RAS versus standard of care (PT/OT) over the course of 6 months, beginning at least 3 months after stroke onset.

Based on evidence suggesting poorer functional outcomes linked with hemorrhagic-type cerebellar stroke,[17,18,33] randomization into experimental and control groups will be stratified by stroke type (ischemic versus hemorrhagic). Randomization will be centrally accomplished using a computerized random selector program implemented by a computer specialist external to the study. Each patient will be assigned a unique study number as well as a computer-generated randomized treatment plan, which will be distributed by sealed envelopes to study personnel at each treatment facility regarding each enrolled subject.

A multi-center design will be implemented to ensure an appropriate number of participants and increase generalizability of study results. Accounting for possible drop-out, predicted at 0-13%,[83,122] target enrollment will be 840 patients. This allows for a conservative 15% drop-out rate. A minimum sample size of n = 730 patients was determined for this study based on calculations for a minimal clinically important difference (MCID) of 2%, power of 90%, and alpha of 0.01 (2-tailed). Participants will be consecutively recruited from participating stroke centers and stroke rehabilitation centers, primary care providers, neurologists, and stroke support groups, over 12 months until sample size is achieved.

Study duration includes a recruitment period of 12 months. Treatment will be administered on an outpatient basis over a 6-month intervention period, beginning at a minimum of 90 days after stroke onset.

### 2.2.2 Patient Selection

Eligible participants are ≥ 18 years of age with history of ischemic or hemorrhagic cerebellar stroke, verified by CT or MRI, with persisting associated functional impairment and ataxia as indicated by an mRS score of 3-5 and SARA score of 5.5 or greater, respectively.[123] Time from stroke must be ≥ 90 days, consistent with data indicating a plateau in motor recovery at this time in patients treated with standard of care.[37-40] Patients must be able to hear and/or respond to verbal stimuli. Participants must possess an appropriate level of alertness defined by a mini-mental state examination (MMSE) score greater than 24.[87,124]

Patients excluded from this study include those not able to meet inclusion criteria; those with prior neurological or communication disorders, hearing disorders, or severe dementia, causing an inability to meet intervention demands in experimental or standard of care conditions.[61] Also excluded are those with visual, vestibular, or orthopedic injuries influencing balance and gait.[21] Patients with prior hemispheric stroke are excluded to avoid possible confounding of results; and, patients with a pre-stroke mRS score ≥ 3 are excluded, as they are theoretically unable to achieve favorable post-training outcomes.[105]

### 2.2.3 Clinical management

Music therapy is safe and is not associated with any risks other than routine risks relating to PT and OT. There is no need for additional monitoring outside of pre-existing healthcare providers. Like other rehabilitative approaches, RAS involves motor training and

exercises, which may increase risk of falls in some patients. All training sessions will be attended by certified physiotherapists in the case that gait impairments pose risk for falls.

### 2.2.4 Experimental Condition

#### Training protocols

The experimental intervention consists of gait training with RAS. Training with RAS will be conducted in 30-minute sessions, consistent with studies on RAS in stroke and other movement disorders.[58,75,76,125,126] Sessions will take place at designated rehabilitation centers experienced in management of stroke patients. The first and last 5 minutes of each session will be devoted to a warm up and cool down, respectively. A warm up period of 2-5 minutes is believed to increase adaptability to RAS and allow practice with the delivered beat.[112,127,128] After warm up, participants will perform five, 2-minute gait trials at the determined RAS cadence. Each trial will be followed by a 2-minute rest period (Appendix A).

Consistent with research on RAS in chronic stroke patients,[59] preferred walking cadence will be determined prior to the start of gait training, using the 10-meter walking test, which has been recognized for high test-retest reliability in patients with stroke (ICC = 0.87).[129] The test requires participants to walk comfortably along a 5-meter pathway, forward and then turning to return to the starting position. The procedure is repeated twice, with short rests between trials. Total time is recorded for the completion of each 10-meter trial, omitting the time taken to turn. The average of 10-meter trials will be used to generate individual baseline cadence, which will be adapted to RAS protocol and accompanied by music – either pop or classical – according to patient preference. The test will be repeated at 3 months and at the 6-month conclusion of the training protocol.

#### Selection of tempo and tune

Studies exploring RAS-facilitated motor benefits in patients with cerebellar stroke have observed greater functional improvement with delivery of beat cadences slightly above baseline cadence. Delivery of RAS at 110-130% cadence has been associated with significant motor improvements, compared to RAS at 100% (baseline) tempo.[114,128] Thus, as in other studies using RAS in stroke patients, tempo will be sequentially increased over the course of the study.[59,60] Training sessions will be divided into monthly blocks, with incremental 5% increases in rhythm frequency implemented upon the beginning of each new block as tolerated (Appendix B). Evaluations of mRS and SARA scores will be conducted on the final day of each training block, in place of normally-scheduled gait training sessions.

Evidence that RAS may facilitate gait improvement beyond a 90-day acute period is supported by work by Oh et al. (2015). Researchers evaluated differences between RAS using music versus metronome to improve gait parameters in patients with chronic stroke. After four weeks of training, patients in the music group exhibited significant improvements in gait velocity and cadence, and deviations in body sway and functional gait assessments, compared to patients trained with metronome alone ($p < 0.05$).[130] Music therapy is believed to involve motivational effects that may influence training adherence and outcomes. Factors such as familiarity and "groove" – defined as the ability of music to elicit a desire to move – point to motivational elements of music, producing greater tempo matching ($p = 0.008$) and gait velocity ($p = 0.009$) in healthy patients, versus low-familiarity, low-groove music.[131] To incorporate these possible musical effects, RAS will be delivered through rhythmically-accentuated music, which will be used repeatedly to ensure familiarity over the course of the study. Repeated use of one musical template has the additional benefit of ameliorating distraction associated with musical novelty, which has been suggested in studies of RAS in patients with Huntington's disease to hinder acquisition of motor improvements.[81]

Duration of training

Studies on RAS in hemiparetic stroke suggests increased benefits with longer training periods. Thaut et al. (1997) implemented RAS for a 6-week period in stroke patients during the acute phase, compared with stroke patients undergoing training without RAS. At the study conclusion, patients trained with RAS exhibited significant increases in gait velocity ($p < 0.05$), stride length ($p < 0.02$), and symmetrical EMG activation of the gastrocnemius ($p < 0.02$).[59] An identical protocol was implemented by Thaut et al. in 2007, comparing RAS to neurodevelopmental (NDT)/Bobath therapy, that revealed similar gait improvements in patients with RAS over the Bobath approach. Percentage improvements in gait parameters achieved over 3 weeks were subjectively less than those seen during the 6-week study, suggesting added motor benefits with longer duration of RAS interventions.[132] Notably, both studies were conducted on hemiparetic stroke patients within the acute recovery phase. Additionally, the 6-week study was conducted in an inpatient hospital setting, with patients undergoing twice-daily training, five days per week, for a total of 60 sessions in 6 weeks. Interventions during the 3-week study were also conducted five days per week, but occurred just once per day, for a total of 15 sessions. This may account for the reduction in outcome.

This proposed study implements less frequent training sessions over a six-month period, to maintain patient adherence and allow time for functional gains and differences between treatment allocations to manifest. Most outpatient rehabilitation programs occur two-to-three times weekly. Gait training with RAS three times per week allows for a total of 72 sessions over 6 months. As there is some dispute regarding the length of the acute recovery period, with some studies suggesting that spontaneous gains may be possible up to 15 weeks post-stroke,[133] the 6-month duration of this study allows for plateau of any residual spontaneous gains between 3 and 6 months, while still preserving time for recognition of

effects. A 6-month intervention also allows for observation of effect trends, and evaluation if benefits facilitated by RAS are subject to plateau or deterioration over time.

### 2.2.5 Control Condition

The control condition consists of physical and occupational therapies which constitute the current standard of care for stroke rehabilitation. Rehabilitation therapies will be administered for the same amount of time as the RAS condition and will follow identical protocols for warm up, cool down, active training, and rest periods. Physiotherapists will be instructed to apply similar instructions about gait parameters to practice, but without RAS.

### 2.2.6 Primary outcomes

Ataxic symptoms will be assessed using the Scale for Assessment and Rating of Ataxia (SARA) while functional impairment will be measured by the Modified Rankin Scale (mRS). The SARA is an 8 item, 40-point performance scale of motor aberrations, with a total score of 0 indicating no ataxia/normal, and a score of 40 indicating most severe ataxia. The SARA scale has been clinically validated as a reliable measure of ataxia after stoke. It is directly correlated with abnormal gait status ($p < 0.01$) and ability to perform daily activities ($p < 0.01$).[123] SARA scores under 5.5 represent minimal functional dependency, while those over 23 indicate total dependency.[123] The ICARS scale, despite being a similarly validated assessment tool, was not chosen to evaluate ataxia in this study, as it has been criticized for difficulty due to its length, redundancy, and clinical impracticality.[134] In addition, the SARA – but not ICARS – has been correlated with the mRS, which has been used routinely in chronic cerebellar stoke to describe functional status. Choi et al. (2018) evaluated the utility of the SARA in addressing clinical features of stroke patients at discharge, and found the SARA to be sufficient to predict mRS value ($p < 0.001$). Thus, while few studies have

utilized the SARA as a measure of ataxia in chronic cerebellar stroke, correlation between the SARA and the mRS allows for extrapolation of mRS findings in this population.

The mRS score best serves as a measure of the primary outcome. It has been used in research on chronic cerebellar stroke, and has been associated with fall risk and long-term morbidity in stroke. Work by Callaly et al. (2015) followed stroke patients for up to 2 years post-stroke, describing the rates of falls, fractures, and injuries, in a prospective population-based study. Researchers classified patients according to mRS at day 90, with mild-moderate disability categorized as mRS 2-3, and severe disability as mRS 4-5. Upon follow-up at 2 years, over 30% of surviving patients had fallen, and over 60% had fallen two or more times. Nearly a quarter of falls resulted in fracture. Analysis by mRS categorization revealed that, of the total cohort, patients with mRS of 2-3 (indicating impaired mobility) had the highest risk of falling within two years (OR 2.3, $p = 0.003$). In 2-year survivors, mRS of 4-5 (functional dependence) was associated with the highest independent risk for falling within two years (OR 2.7, $P = 0.003$).[135] The direct correlation between mRS score and both fall risk and mortality makes this rating an important prognostic factor.

Prior studies in patients with chronic stroke have demonstrated RAS-facilitated improvements in gait patterns that translate to significant improvements in mRS-defined functional independence. For the mRS, the minimal clinically important difference (MCID), defined as the smallest change in a treatment outcome that a patient or care provider would consider worthwhile, has been represented as a 1-point change in mRS score.[136,137] Within the context of post-stroke gait impairment, Tilson et al. (2010) observed that an increase in comfortable gait speed of at least 0.16 meters per second produced the best combination of sensitivity (73.9%, 95% CI = 65.9% - 80.6%) and specificity (57.0%, CI = 49.0% - 64.7%) for detecting mRS score improvement.[138] Fulk et al. (2018) drew similar conclusions while

implementing the six-minute walk test (6MWT) in patients at two months post-stroke. Based on mRS predictive value, increases in walking speed of at least 0.19 meters per second were correlated with improvement in mRS of 1 or more points. In patients with slower baseline walking speed (under 0.40 m/s), a 0.12 m/s change in speed was associated with mRS functional improvement.[137] Use of RAS in patients with chronic cerebral stroke has induced changes in gait speed at this level, in excess of those facilitated by conventional therapy.[59,60,124] It is worthwhile to note that a 1-point change in mRS does not mean that a patient will change categorization of functional status. For example, a patient with an mRS score of 5 prior to intervention, who is scored at 4 following intervention, can experience clinically significant improvement, but will remain in the "poor outcome" category.

### 2.2.7 Secondary outcomes

Fall incidence over the study will be assessed as a secondary outcome. Monthly fall assessment will be conducted in questionnaire format at the end of each intervention block as part of the ataxia and functional status assessment. This will address the number of falls and related consequences. Definition of falls as used in prior studies is, "an event reported by the faller or a witness, resulting in a person inadvertently coming to rest on the ground or another lower level, with or without loss of consciousness or injury."[139]

### 2.2.8 Sample size rationale

A sample size of 730 participants will be required to detect a 2% difference in proportion of patients achieving clinically significant functional improvement between RAS and standard of care conditions. This sample size was calculated for a two-tailed test with an alpha of 0.01 and beta of 0.1 to achieve a confidence level of 99% and power of 90%. A total of 840 subjects will be enrolled to account for a 15% attrition rate (Appendix C).

A 2% effect size was determined using "Minimal Clinically Important Difference," (MCID) in stroke patients. In the context of stroke outcomes at 90 days, 11-15 patients, per 1000 treated, would need to benefit (by achieving freedom from disability, as defined by an mRS of 0-2) for an intervention to be of significant benefit to use in clinical practice. Converted to a natural base value, the MCID for the mRS in the context of acute/subacute stroke is 1.1-1.5% of patients.[140] Extrapolation of MCID to patients in the chronic phase allowed for the conservative determination of a 2% difference in effect for mRS outcomes.

An attrition rate of 15% is based on adherence observed in other long-term studies of interventions for chronic stroke patients. Studies utilizing RAS for gait recovery in patients with chronic cerebral stroke have been conducted with little patient drop out, with attrition rates of just 1-2%.[127,130] Much existing work on RAS in chronic stroke has produced promising outcomes, which likely contributes to patient adherence. However, many of these studies are conducted over periods of 4 or 6 weeks. Patient adherence to rehabilitation after stroke is observed to fall with time, and improvement plateau is thought to contribute to this pattern.[141] In research by Wu et al. (2015), intensive rehabilitation therapy was compared to usual care in chronic stroke patients. At 12 weeks, motor benefits were seen in the intensive therapy group, and an attrition rate of approximately 6% was observed. At 36 weeks, motor gains had attenuated, and attrition had risen to nearly 13%.[122] As there is an inherent attrition rate related to a plateau effect in improvement when using conventional rehabilitation techniques, a predicted attrition of 15% was assumed to match observations from other studies. As a note, higher attrition rates of 28% have been recorded in studies of similar duration, but include patient death within reasons for loss to follow up.[40] Patient death most often occurs during the acute or subacute phase after stroke.[142] As this study is designed to assess chronic stroke patients, lower drop-out rates were assumed for this population.

### 2.2.9 Estimated recruitment sites

Participants will be consecutively recruited from participating tertiary stroke rehabilitation centers, primary care providers, neurologists, and stroke support groups, over the course of 12 months until adequate sample size is met. Initial contact sites are those within a 25-mile radius of the central data collection and processing location at the Yale School of Medicine, for ease of communications and management. Recruitment will be assessed quarterly throughout the 12-month period, with expansion of radius to include additional sites as needed to obtain adequate sample size.

### 2.2.10 Confounding

Stratified randomization will be implemented to produce groups comparable at baseline, thus reducing the risk of confounding in the relationship between RAS and primary outcomes. An analysis of covariance (ANCOVA) and multivariate regression analysis will be included as parts of secondary analyses, to evaluate for significant external influences and possible confounding. Unmodifiable characteristics that may influence results that will be subject to secondary analysis as described, include: gender, age, education level, musical experience, cerebellar lesion size and location, hemorrhagic versus ischemic stroke origin, concurrent hemiparesis, presence of complication (edema, herniation, hydrocephalus, brain stem involvement), surgical intervention, and inpatient length of stay.

## 2.3 Conclusion

The cerebellum performs a key role in neural circuits involved with sensory and motor function. Models of cerebellar organization postulate feed-forward and feedback mechanisms by which the cerebellum analyzes and facilitates coordinated movement, as well

as acquisition and automatization of motor tasks. Focal cerebellar lesions are associated with motor abnormalities, most classically ataxia, as well as deficits in procedural learning. These impairments appear to be non-resolving with time. A population of cerebellar stroke patients experience chronic motor deficits including ataxia, which is associated with impairments of gait and functionality, and increased risk of falls. Falls and mortality are associated with poor functional status as assessed by the Modified Rankin Scale (mRS), which clinically correlates with degree of ataxia as assessed by the SARA evaluation in chronic stroke.

Current standards of care for stroke rehabilitation including PT and OT have been unsuccessful in ameliorating chronic functional and motor impairments in patients following stroke; and, most functional gains are believed to occur within 90 days of stroke. Music therapy is a promising rehabilitative strategy, and evidence suggests that RAS may facilitate gait improvements in chronic hemiparesis in stroke patients, as well as patients with PD, MS, CP, and HD. There is a paucity of research evaluating the utilization of RAS in cerebellar stroke, and essentially none regarding RAS for cerebellar stroke in the chronic phase.

Observed gait improvements in subjects with vascular-related hemiparesis and motor deficits due to other neurological pathologies are encouraging for the use of RAS in patients with cerebellar stroke. The cerebellum is implicated in contributing to motor recovery in neurologic conditions including cerebral stroke and PD, MS, CP, and HD. But, direct injury to the cerebellum may negatively impact the benefits for therapy. Postulated roles of the cerebellum in sensorimotor learning have led some to doubt as to whether patients with chronic cerebellar stroke are able to acquire motor learning skills associated with RAS. The current study seeks to determine if there is a significant benefit to RAS therapy in facilitating motor recovery, as evaluated by SARA and mRS, in patients with chronic cerebellar stroke.

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# CHAPTER 3: METHODS

3.1 Study design

This is a multi-center, two-group parallel randomized control trial to compare improvement of ataxia and functional status in chronic cerebellar stroke across patients receiving RAS versus standard of care (PT/OT) over the course of 6 months.

3.2 Procedures and site selection

Prior to the start of recruitment, IRB approval will be obtained for each rehabilitation training site. Approval from the IRB and Human Investigation Committee at Yale University will also be obtained. Eligible patients will be consecutively recruited from participating tertiary stroke rehabilitation centers, primary care providers, neurologists, and stroke support groups, over the course of 12 months until a sample size of 840 is met.

A letter (Appendix D) will be sent to clinical service lines (e.g. neurology services, primary care providers, etc.) to outline the study and encourage referral of patients who may be eligible for participation. Participating offices and providers will be asked to assist with identification and enrollment of eligible patients for the study.

Recruitment sites will be visited by research assistants to facilitate the site enrollment process. Assistants will be responsible for conveying information regarding the protocol with physicians and staff of recruitment sites, in order to facilitate the proper identification and enrollment of eligible participants who meet inclusion and exclusion criteria.

The process of patient recruitment and enrollment is illustrated by CONSORT diagram (Appendix E). Patients found to be potential subjects for the study will be identified by providers at selected recruitment sites and provided general information on the proposed study. If the patient is interested in participating, the research assistant will be provided with the patient's contact information, and will set up a telephone call to conduct a structured

screening interview (Appendix F) to determine participation eligibility. Patients believed to be potentially eligible participants will then be scheduled for a formal evaluation of ataxia and functional status and determination of whether eligibility criteria is met.

Research assistants will assist in obtaining informed consent from subjects approved to participate. They will facilitate communication with central study coordinators during the recruitment phase and will continue to relay information between study sites and central coordination during the intervention period, including collection of monthly patient outcome assessments.

3.3 Study population and sampling

Eligible participants are ≥ 18 years of age with chronic ischemic or hemorrhagic cerebellar stroke defined as stroke onset ≥ 90 days prior, verified by CT or MRI, resulting in functional impairment and ataxia as indicated by a Modified Rankin scale score of 3-5, and a SARA score of 5.5 or greater.

Eligible subjects who meet inclusion criteria and no exclusion criteria (Appendix G) will be provided written consent forms (Appendix H). Consent forms include study description, duration, potential risks and benefits, and explain that participation in the study is voluntary and may be terminated at any time by the patient. Consent will be obtained in writing. If the patient is unable to write legibly due to motor impairments associated with stroke, verbal consent will be obtained with a verified witness present. Consenting patients will be enrolled consecutively as they are identified over 12 months, with intervention and assessments occurring over a 6-month period.

3.4 Subject confidentiality

An informed consent will be obtained, which will authorize researchers to access personal health information (PHI) of patients. This consent will detail intended uses and limitations to access PHI in accordance with HIPAA regulations. Only pertinent health information will be reviewed and collected. All patient information used during the course of the study is confidential, and will be accessible only to authorized research personnel who have completed a HIPAA privacy training course prior to handling PHI.

Each participant will be assigned a unique identification number upon enrollment in the study. All patient data, including extracted PHI and information gathered during the course of the study, will be labeled with this number. The key to this unique identification will be logged into a database to separate patient information from identity. A separate excel file will be created to contain unique patient identifiers and personally identifiable information. This file will be secured by password and network-protected firewall. All hard-copy and paper materials will be kept in a secure central location accessible only to approved study personnel. At the conclusion of the study, all related documents and any PHI extracted will be appropriately shredded and discarded in accordance with HIPAA standards.

3.5 Study variables and measures

Dependent variables

Primary outcomes: differences in patient ataxia scores as evaluated by the scale for the assessment and rating of ataxia (SARA), and level of functional independence as assessed by the Modified Rankin Scale (mRS). SARA scores run from 0-40, with 0 indicating no ataxic symptoms and 40 indicating the most severe ataxia (Appendix I). Assessments using the mRS of 0-6 will be dichotomized, with scores of 0-2 indicating "good" functional status

and scores of 3-5 indicating "poor" functional status. A score of 6 is given in the case of patient death (Appendix J). Initial assessment of SARA and mRS scores will be made during the recruitment phase, in order to identify eligible participants, with an additional pre-intervention assessment for enrolled patients conducted 1 week prior to the beginning of the intervention. Final assessments will be made on the final day of the intervention, following 6 months of training. Differences will be calculated as pre-training minus post-training scores. Additional evaluations of SARA and mRS status will be made at the conclusion of each training month, to evaluate for possible group-by-time interaction effects.

A secondary outcome of fall incidence will be included. Monthly fall assessment will be conducted in questionnaire format, during end-of-block patient visits for SARA and mRS assessment, to determine number of falls and related consequences (Appendix K).

Independent variables

Independent variables: the treatment arm to which the patient is assigned. Patients will be randomly assigned to receive gait training with RAS (treatment group), or standard of care consisting of PT and OT (control group).

Other descriptive measures

Baseline patient characteristics (Appendix L) known to be independently associated with the dependent variables, as well as any variables found to vary significantly between groups will be subject to secondary analysis of covariance (ANCOVA) and multivariate regression.

## 3.6 Methodology considerations

Delivery of rhythmic auditory stimulation (RAS)

Gait training with RAS will be conducted by a set of board-certified music therapists engaged for this study, who have agreed to the delivery of therapy following specific protocols determined for this study (Appendix M). RAS will be delivered only to patients to whom they are assigned. Patients will undergo evaluation of SARA and mRS scores by independent, blinded assessors prior to starting RAS.

Patients will receive three, 30-minute sessions of RAS per week over the course of 6 months, for a total of 72 sessions. Sessions will begin within 1 week of pre-intervention SARA/mRS evaluation. Content of each RAS session will consist of five, 2-minute gait trials at a determined RAS cadence, interspersed with 2-minute rest periods between trials, and 5-minute warm up and cool down before and after training.

RAS sessions will be conducted at outpatient rehabilitation clinics and attended by physiotherapists to ensure patient safety. Patients will undergo monthly evaluations of SARA and mRS scores by independent, blinded assessors over the study course; the final session of each month will be dedicated to SARA and mRS evaluation.

Delivery of standard of care (PT/OT) and Assessors

Standard of care will consist of physical therapy (PT) and occupational therapy (OT), provided by board-certified physical and occupational therapists. Patients will undergo evaluation of SARA and mRS scores by independent, blinded assessors prior to starting PT/OT.

Patients will attend three, 30-minute PT/OT sessions per week over the course of 6 months for a total of 72 sessions. Sessions will begin within 1 week of pre-intervention SARA and mRS evaluation. PT and OT will be delivered according to the level and needs of the patient, and designed to facilitate stroke rehabilitation with focus on gait improvement, with the exclusion of RAS.

Ratings done throughout the study will be conducted by independent assessors. These assessors will be recruited to participate in the study and will be required to hold active board certification in physiotherapy. Assessors will rotate amongst treatment sites, so that no two assessments on the same patient are completed by the same assessor. Patients will be asked not to disclose details of their treatment to outcome assessors. Statistical analyses will be conducted by an independent central study coordinator, blinded to treatment group interventions. Patients will undergo monthly assessments using the SARA and mRS rating scales. At month 0, 3, and 6, the 10-meter walking test will also be administered.

### 3.7 Randomization procedure and assignment of intervention

Randomization into experimental and control groups will be stratified by stroke type (ischemic or hemorrhagic) and will be centrally accomplished using a computerized randomization program implemented by a computer specialist external to the study. Patients will be randomly assigned a unique, computer-generated random subject number that will also indicate their intervention group. Patients and therapists cannot be blinded to the intervention assignments. Research assistants will facilitate coordination with the proper treatment site, once the patient has been assigned to his/her treatment allocation. At each site, administrative staff not involved in the treatment will help to coordinate scheduling of treatment in the outpatient setting. Staff will also work to schedule monthly SARA and mRS assessments with blinded assessors who have no role in patient therapy.

### 3.8 Blinding

Over 6 months, patients will be administered therapy by a single physical or musical therapist chosen from a pool of therapists selected for the study, all with comparable

experience in stroke rehabilitation. Outcomes will be assessed by independent assessors blinded to patient group, baseline and stroke characteristics, and previous assessment scores.

### 3.9 Adherence

Patients will receive communication via preferred method (text, phone call, email) from research assistants 3 days prior to each scheduled session as a reminder. Patient attendance will be recorded by scheduled therapists and research assistants. Date of session, duration, and clinical notes for each session will be recorded by therapists.

### 3.10 Monitoring of adverse events

Patient deaths and adverse events (e.g. falls) will be assessed monthly. Failure to attend scheduled sessions will result in a phone call inquiry as to the cause of absence. Repeated failures to attend scheduled sessions or cancellation of 50% or more of scheduled sessions will be considered a study drop-out and the subject will be unenrolled. Failure to attend monthly rating sessions with independent assessors will be rescheduled within one week of the missed date. Absence from more than 50% of the monthly rating sessions with independent assessors will be considered a drop-out and the subject will be unenrolled.

### 3.11 Data collection

All data will be collected within 2 years of the study start date, including the 12-month recruitment period and 6-month training time and assessments of last recruited subjects. Baseline patient characteristics, stroke characteristics, and relevant hospitalization and therapy dates will be collected and compiled. Patient assessment scores will be entered into data collections as they are made available, along with information on falls or adverse events. Clinical notes by music therapists and physiotherapists will also be entered into this

database. Information will be transferred by an independent research associate not involved elsewhere in the study to transfer relevant data into a spreadsheet for statistical analysis.

3.12 Sample size calculation

Sample size has been determined using an online calculator developed by Bespoke Statistical Services to determine a sample size sufficient to power a study at 90% with a confidence level of 99%. Based on research previously presented, we expect that between assessments at baseline and 6-months, patients undergoing standard PT and OT will not experience any absolute gains in ataxia (SARA) or functional independence (mRS) scores. Essentially, rating scores for patients in the control group are expected to remain not significantly improved; at baseline or worse. Based on an MCID of the mRS of approximately 1.1-1.5%, a conservative 2% difference in effect for patients undergoing RAS training is assumed. Using these values, we determine a total of 730 subjects must complete the primary study endpoint and be usable in analysis in order to detect an effect.

Accounting for completion rates reported in the literature for this population, we expect at least 85% of patients with ataxia and functional dependence to complete the study. Thus, recruiting is scaled up to a total of 840 with 420 patients per arm.

3.13 Analysis

Statistical analysis will be conducted using computer-based software. The level of statistical significance for all tests will be set to 0.01. Analyses will be performed using an intention-to-treat analysis. A repeated measures ANOVA will be used to evaluate differences in SARA scores between groups at pre- versus post-training and during monthly evaluations throughout the study period. Repeated Chi square analyses will be used to assess differences in mRS scores over this time. Incidence of falls over the course of 6 months will be

compared between groups using a negative binomial regression model.[1] These analyses will allow for evaluations of overall differences of effect between groups following completion of training interventions, and assessment of group-by-time interactions throughout the study.

Statistical analyses will be further stratified by patient age (under 50 years old, age 50-59, age 60-69, age 70-79, and age 80 or greater)[2] and time from stroke onset (3 months to 1 year, 1 to 2 years, and greater than 2 years).

Baseline characteristics independently associated with the dependent variables, as well as any variables determined to vary significantly between groups, will be subject to post-hoc analysis upon study completion. An analysis of covariance (ANCOVA) and multivariate regression analysis will be included as parts of secondary analyses, to evaluate for any significant external influences and possible confounding.

3.14 Timeline

Duration of the study, including patient identification and enrollment, experimental interventions, and data analysis, is 24 months. Recruitment will occur over a 1-year period, with initiation of interventions occurring on a rolling basis as patients are enrolled. All interventions will conclude by 1.5 years, allowing for an approximate 6-month period of time dedicated to data analysis and interpretation (Appendix N).

3.16 Resources & Personnel

Principle Investigators: Kaitlin Fitzgerald, PA-S; Dr. Diana Richardson, MD; Responsible for oversight of all operations, ensuring appropriate clinical practice and ethical soundness. Therapists: board-certified physical and occupational therapists, and board-certified music therapists familiar with the implementation of RAS will undergo training on the intervention the protocols for standardization of treatment interventions. At the time of site enrollment,

they will be familiarized with study protocol. All therapists will be selected on the basis of comparable experience in rehabilitation of stroke patients.

Site Primary Investigators (PI): site investigators are responsible to enroll subjects and ensure adherence to the protocol. They are responsible for ensuring that all participating study personnel and therapists at their sites are familiar with the study protocol. Site PI will collect and convey study data for delivery and monitoring of interventions, as well as record appointment details including date of session, duration, and clinical notes.

Research Assistants: responsible for visiting recruitment sites and conveying information regarding the study to medical providers/staff to facilitate identification of eligible participants. These individuals will provide study-related documents to participating sites; serve as a point of contact for study personnel; provide regular appointment reminders to subjects; and, conduct phone call eligibility screening. Research assistants will relay information between study sites and central coordination during the study period, including collection of monthly patient assessments and notes. They will conduct inquiries regarding missed appointments and monitor for minimum compliance to maintain enrollment.

Independent Assessors: responsible for evaluation of patient SARA and mRS scores when determining eligibility during enrollment, at baseline, monthly during the 6-month intervention, and at the study conclusion. Assessors are blinded to assigned intervention groups, baseline symptomology, stroke localization, and previous assessment scores.

Data Analyst: responsible for analysis of clinical data.

HIPAA training*:* to be provided by Yale University to all research personnel involved in the access and handling of personal health information (PHI).

Facilities: rehabilitation interventions will be conducted at enrolled outpatient rehabilitation clinics in the community.

3.2 References

1. Robertson MC, Campbell AJ, Herbison P. Statistical Analysis of Efficacy in Falls Prevention Trials. *The Journals of Gerontology: Series A.* 2005;60(4):530-534.
2. Bagg S, Pombo Alicia P, Hopman W. Effect of Age on Functional Outcomes After Stroke Rehabilitation. *Stroke.* 2002;33(1):179-185.

# CHAPTER 4: CONCLUSIONS

### 4.1 Advantages

This study has several strengths. Music therapy and RAS are safe, and pose no additional risk to patient health over routine therapeutic interventions. RAS is inexpensive and can easily be incorporated into existing therapeutic practice at rehabilitation facilities. There is additional potential for this therapy to be conducted within the home, using self-training videos or telemedicine. The use of home-based media would further support utilizing electronic media to continue or reinforce therapeutic gains over longer periods of time. There is potential, therefore, for conducting long-term investigations regarding RAS techniques.

This study is designed to minimize variables between intervention groups. This is achieved by stratifying randomization by stroke type and by performing an intention-to-treat analysis to enhance external validity and minimize bias. While this approach is sometimes criticized for reduction in power, this study is powered at 90%, which allows for flexibility.

### 4.2 Disadvantages

This study is limited by its use of convenience sampling, which is vulnerable to selection bias and sampling error. Another source of potential bias is that it is not feasible to conduct this study as a double-blinded, placebo-controlled trial. Subjects and therapists are aware that RAS is not the current standard of care and as such, may confer an implicit bias affecting participation. Conversely, there is potential for enhanced placebo effect from the therapy due to anticipated benefit, which would promote greater effort from subjects and therapists. The use of blinded assessors attempts to mitigate this potential source of bias. With regards to falls, patient self-reporting introduces potential for recall bias or selective reporting. In this study, it is suspected that this might be applicable equally between the two groups. Finally, due to the 2-year duration of this study, data on benefits from longer term intervention and/or retention cannot be

addressed within the scope of this study. There is, therefore, potential for additional investigations on long-term interventions.

# APPENDICES

Appendix A: Single Session RAS Gait Training Protocol

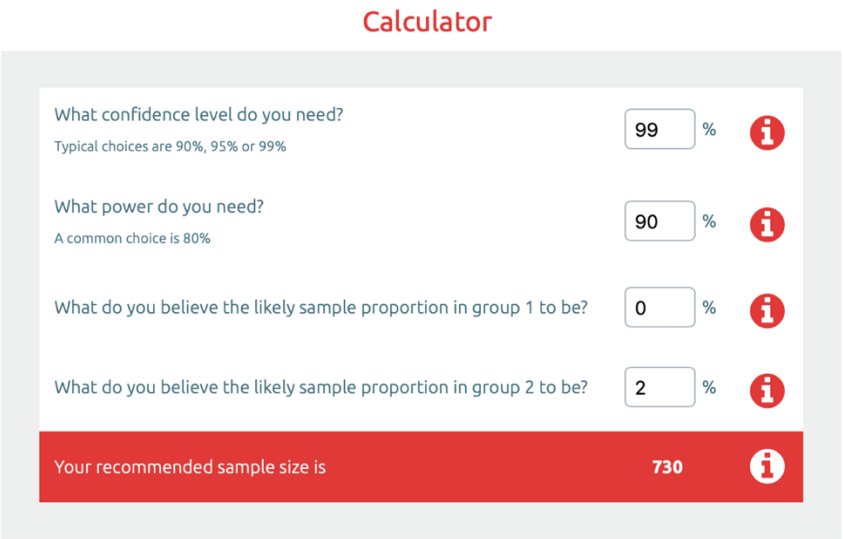
| Time (minutes) | Activity |
|---|---|
| 5 | Warm-up |
| 2 | RAS training |
| 2 | Break |
| 2 | RAS training |
| 2 | Break |
| 2 | RAS training |
| 2 | Break |
| 2 | RAS training |
| 2 | Break |
| 2 | RAS training |
| 2 | Break |
| 5 | Cool down |
| Total: 30 minutes | |

Appendix B: RAS Gait Training and Assessment Schedule

| Pre test | Month 1 | T* | Month 2 | T | Month 3 | T | Month 4 | T | Month 5 | T | Month 6 | Post Test |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10MWT<br>SARA<br>mRS | RAS<br>100% | | RAS<br>105% | | RAS<br>110% | 10MWT | RAS<br>115% | | RAS 120% | | RAS 125% | 10 MWT<br>SARA<br>mRS |

*T = serial, end of month evaluations of mRS and SARA scores
*10MWT = 10-meter walking test

Appendix C: Sample Size Calculation




https://select-statistics.co.uk/calculators/sample-size-calculator-two-proportions/

Appendix D: Letter to Clinical Service Lines

To Whom It May Concern:

We are writing to inform you about an upcoming clinical trial which may be an exciting opportunity to provide new rehabilitative options to patients with chronic ataxia following cerebellar stroke. We would like to offer you the opportunity to refer your patients to participate in this trial, which explores the effect of rhythmic auditory stimulation (RAS) compared against standard of care (physical and occupational therapies) in stroke rehabilitation for patients with chronic ataxia and functional impairment.

For this study, we are recruiting 840 patients who experienced cerebellar stroke at least 3 months ago, and who have persisting ataxic symptoms influencing functional independence. Our inclusion and exclusion criteria is listed below:

**Inclusion**

- Age ≥ 18 years
- History of CT or MRI-verified ischemic or hemorrhagic cerebellar stroke
- Modified Rankin Scale (mRS) score 3-5
- Scale for the Assessment and Rating of Ataxia (SARA) score ≥ 5.5
- Onset of stroke ≥ 3 months ago
- Able to hear/respond to auditory stimuli and verbal instruction
- Mini-mental state examination (MMSE) score ≥ 24

**Exclusion**

- Prior neurological or communication disorder
- Hearing disability or disorder precluding recognition of auditory stimuli
- Premorbid mRS ≥3
- Premorbid SARA ≥5.5
- Prior hemispheric or brainstem stroke
- Inability to meet demands of intervention
- Severe dementia or MMSE < 24
- Visual, vestibular, orthopedic, or other impairment influencing balance and gait

We have enclosed in this letter the patient consent form detailing study design, eligibility, and expectations for participation. We hope that you will take a few moments to review these materials and consider referring patients you believe may be eligible for this clinical study. If you, after having reviewed these materials, are interested in referring patients to this study, we will arrange an in-person visit to your place of work to discuss any further details or questions you may have.

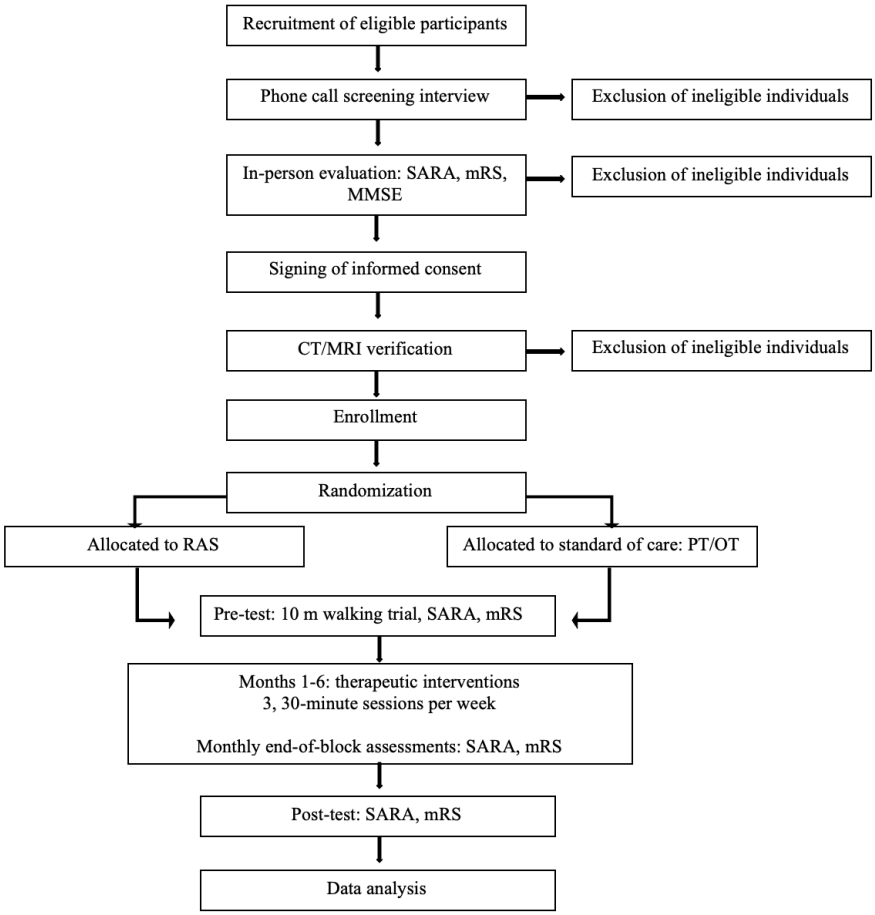
Please ensure all information provided to you relating to this clinical trial is treated with strict confidentiality. Please feel free to contact me if you would like further information about the trial and the potential participation of your patients in the trial.

Thank you for your consideration.

Yours sincerely,
Kaitlin Fitzgerald

Yale University School of Medicine
999-999-9999

Appendix E: CONSORT Diagram of Participant Recruitment and Enrollment



Appendix F: Structured Phone Call Screening Interview

Hello Mr./Mrs. _____,

We are calling you to discuss an upcoming clinical trial which may be an exciting opportunity to provide new rehabilitative options to patients with chronic ataxia following cerebellar stroke. We have been informed by _____ that you may be an eligible subject for participation in this trial and that, after receiving information on the study, you have expressed interest in participating.

Before we schedule an in-person assessment and evaluation for eligibility, we would like to discuss aspects relating to the study over the phone.

1. How old are you?
    a. **Patient must be at least 18 years of age**
2. How long ago was your stroke?
    a. **Stroke onset must be at least 3 months prior**
3. How would you describe your level of disability prior to experiencing stroke?
    a. No or minimal disability
    b. Some disability: I was able to walk unassisted (without assistive device/person), but I needed some help in looking after my own affairs and carrying out my previous activities
    c. Moderate disability: I was unable to walk unassisted, and I needed help managing my daily bodily needs
    d. Severe disability: I needed constant nursing care and attention, I was bedridden

    **Patients with no or minimal disability prior to stroke are eligible for participation**
    **Patients with greater than no or minimal disability prior to stroke are ineligible for participation**

4. How would you describe your level of disability presently?
    a. No or minimal disability
    b. Some disability: I am able to walk unassisted, but I need some help in looking after my own affairs and carrying out my previous activities
    c. Moderate disability: I am unable to walk unassisted, and I need help managing my daily bodily needs
    d. Severe disability: I need constant nursing care and attention, I am bedridden

    **Patients with no or minimal disability are ineligible for participation.**
    **Patients with some or moderate disability are eligible for participation.**
    **Patients with severe disability may be eligible if able to fulfill therapeutic requirements**

5. Exclusion criteria:
    a. Do you have any underlying neurological or communication disorders?
        i. **Patients with underlying neurological or communication disorders are ineligible for participation**
    b. Do you have a hearing disability that might interfere with listening to music?
        i. **Patients with a hearing disability that might interfere with listening to music are ineligible for participation**
    c. Have you experienced any other strokes? If yes, do you know which area of the brain was affected?

i. **Patients with prior cerebral or brainstem strokes are ineligible for participation**

d. Have you ever been diagnosed with dementia?
    i. **Patients with severe dementia are ineligible for participation**
e. Do you have any visual, vestibular, orthopedic, or other impairments that affect balance and ability to walk?
    i. **Patients with visual, vestibular, orthopedic, or other impairments that affect balance and ability to walk are ineligible for participation**

For patients who meet exclusion criteria:

Unfortunately, it appears that you do not fit the criteria we've outlined for the current study. We encourage you to check in regularly with your provider about upcoming opportunities for participation in other research studies, and wish you the best in your healthcare journey.

For patients who do not meet exclusion criteria:

It appears that you may meet the criteria we've outlined for the current study. We would like to perform a more detailed evaluation in person, where we can provide further information about the study.

Appendix G: Inclusion and Exclusion Criteria

| **Inclusion** | **Exclusion** |
|---|---|
| Age ≥ 18 years | Prior neurological or communication disorder |
| History of CT or MRI-verified ischemic or hemorrhagic cerebellar stroke | Hearing disability or disorder precluding recognition of auditory stimuli |
| Modified Rankin Scale (mRS) score 3-5 | Premorbid mRS ≥3 |
| Scale for the Assessment and Rating of Ataxia (SARA) score ≥ 5.5 | Premorbid SARA ≥5.5 |
| Onset of stroke ≥ 90 days ago | Prior hemispheric or brainstem stroke |
| Able to hear/respond to auditory stimuli and verbal instruction | Inability to meet demands of intervention |
| Mini-mental state examination (MMSE) score ≥ 24 | Severe dementia or MMSE < 24 |
| | Visual, vestibular, orthopedic, or other impairment influencing balance and gait |

Appendix H: Informed Consent Forms

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

**YALE UNIVERSITY SCHOOL OF MEDICINE**

**Study Title:** Efficacy of Rhythmic Auditory Stimulation on Ataxia and Functional Dependence Post-Cerebellar Stroke

**Principal Investigator:** Kaitlin Fitzgerald, PA-SII; Diana Richardson, MD
**Phone Number**: 999-999-9999
**Funding:** to be determined

**Invitation to Participate and Description of Project**

You are invited to participate in a research study evaluating whether the use of rhythmic auditory stimulation (RAS) therapy will help improve motor difficulties in patients after cerebellar stroke. This is designed to treat both chronic difficulties when performing usual daily activities (known as function deficits) and unsteady irregular walking (known as gait ataxia). We will be comparing rhythmic auditory stimulation (RAS) therapy to standard rehabilitation techniques used during recovery after strokes. The objective of this study is to determine the effectiveness of RAS as a motor rehabilitation approach for patients with chronic cerebellar difficulties, and to facilitate further improvement of walking and performance of daily activities.

Little is known about how strokes change the function of the cerebellum, but it is believed that patients who suffer from stroke regain little functionality beyond the first three months post-stroke. It is known that the use of standard rehabilitative techniques such as physical and occupational therapy help in recovery of some of the cerebellar function. There is a substantial body of work supporting newer therapy techniques such as RAS in patients with motor disorders including impairments seen following stroke. We believe that RAS may be of equal or greater benefit for helping to improve recovery of functional independence and gait in patients who have chronic cerebellar stroke symptoms.

This consent form will provide detailed information about the research study. A member of the research team will review the form with you and answer any questions that you may have about the study. They will discuss all parts of the research, its purpose, procedures, any risks, and possible benefits. Take as much time as you need before you make your decision. After learning about the study, if you wish to participate, you will be asked to sign this form.

**Description of procedures**

Individuals who choose to participate in this study will be randomly assigned to the intervention group receiving RAS, or to the standard of care group receiving more traditional physical and occupational therapy. Training sessions will take place at selected sites staffed by certified therapists (physical, occupational and music therapists). The time dedicated to the study is the same for participants in both treatment groups.

Each participant will participate in pre-determined therapy techniques based on their assigned intervention group. Therapy sessions will be conducted three times per week over 6 months, for a total of 72 sessions. Each session will take approximately 30 minutes. Pre- and post-training assessments of gait and functionality will be performed prior to the start of training, and on the final training day. Monthly evaluations will be conducted throughout the duration of the study.

This study involves frequent training visits to participate in rehabilitation. You will receive communication via preferred method (text, phone call, email) from research assistants 3 days prior to each scheduled session as a reminder.

**Why is this study being offered to me?**

You are being asked to participate in this study because you have a prior diagnosis of cerebellar stroke occurring at least 3 months ago, and have experienced associated persistent impairments in functional independence and gait. We are looking for 840 participants to be part of this research study.

**Risks**

There are no special or anticipated increased risks associated with RAS as a therapeutic modality. Like other rehabilitative techniques, therapy using RAS involves motor training and exercises, which may increase risk in falls in some patients. A certified physiotherapist will be present during all training sessions to prevent and to provide care in the event of a fall.

**Benefits**

Benefits of the study may include improvement in functional status and enhanced recovery of normal gait. Improvements in gait are associated with decreased risk of falling and fall-associated consequences, including death. Information collected from you during the study may help us to better understand the nature of cerebellar stroke, and may highlight new paths for treatment during the chronic phase of recovery, as this is a period of time well-recognized as one in which few functional improvements are gained with standard rehabilitation approaches.

**Economic considerations**

There is no cost to you or your health insurance provider for participation in this study. You will be compensated for costs of travel and parking associated with training visits.

**Treatment alternatives**

One alternative to this study is not to participate. You may also choose to pursue other rehabilitation techniques, which may or may not facilitate personal motor recovery.

**Voluntary participation**

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. Should you decided to participate in this study, you can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

**Confidentiality**

Throughout the course of this study, all information collected about you will be kept confidential, and only accessible by a number assigned to you upon enrollment. In accordance with HIPAA regulations, only relevant health information will be reviewed and collected from your records for the purpose of this study. All information used during the course of the study is confidential, and will be accessed only be individuals authorized by study and with completion of certified HIPAA privacy training course through Yale University.

To ensure security of participants' data, all digital information is to be stored on a secure computer server. All hard-copy and paper materials will be kept in a secure central location accessible only by approved study personnel. All identifying health information extracted as part of the study will be destroyed following conclusion of the study, rendering the data anonymous. It is possible that this anonymous data may be used in subsequent research or distributed to another investigator for future studies without additional informed consent.

Any personal health information or identifiable information obtained in connection with this study will remain confidential except in the event that you wish to disclose it, or its release is required by state or federal law.

**What Information Will You Collect About Me in this Study?**

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. If you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical/laboratory records of services provided in connection with this study
- Research records and medical records created during the study
- Records about phone calls, texts, or email communications made as part of this research
- Records about your study visits
- Information obtained during this research regarding
    - New or worsening motor function
    - Falls and fall-associated consequences
    - Relevant physical exam and test results
    - Diagnosis and management of new health conditions

**How will you use and share my information?**

We will use your information to conduct the study described in this consent form.
We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Health care providers who provide services to you in connection with this study
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan
- Co-Investigators and other investigators
- Study coordinators and members of the research team
- Data and safety monitoring boards and others authorized to monitor the conduct of the study

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

**Why must I sign this document?**

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

**What if I change my mind?**

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to Kaitlin Fitzgerald at 999 Yale University, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to ensure the integrity of the study and/or study oversight.

**What if I want to refuse or end participation before the study is over?**

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

**What will happen with my data if I stop participating?**

Should you choose to withdraw from this study before its completion, data derived during the course of research will be de-identified and thus, rendered anonymous. Data will be unable to be withdrawn.

**Who should I contact if I have questions?**

Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call the Principal Investigators Kaitlin Fitzgerald, PA-S or Diana Richardson, MD at 999-999-9999.

If you have questions about your rights as a research participant, or you have complaints about this research, you can call the Yale Institutional Review Board at (203) 785-4688 or email hrpp@yale.edu.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

**Authorization and Permission**

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

| Participant Printed Name | Participant Signature | Date |
|---|---|---|
| Person Obtaining Consent Printed Name | Person Obtaining Consent Signature | Date |

Complete if the participant is not able to write legibly. This form should be signed by the research assistant delivering information about the research study, as well as a witness.

Print name of research assistant: _____

Signature of research assistant: _____ Date: _____

**An oral translation of this document was administered to the participant by a research assistant proficient in English.**

Print name of impartial witness: _____

Signature of impartial witness: _____Date: _____

Appendix I: Scale for the Assessment and Rating of Ataxia (SARA)

Rater: _____ date: _____ patient: _____

## Scale for the assessment and rating of ataxia (SARA)

### 1) Gait

Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.

0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)
1 Slight difficulties, only visible when walking 10 consecutive steps in tandem
2 Clearly abnormal, tandem walking > 10 steps not possible
3 Considerable staggering, difficulties in half-turn, but without support
4 Marked staggering, intermittent support of the wall required
5 Severe staggering, permanent support of one stick or light support by one arm required
6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)
7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)
8 Unable to walk, even supported

**Score** _____

### 2) Stance

Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.

0 Normal, able to stand in tandem for > 10 s
1 Able to stand with feet together without sway, but not in tandem for > 10s
2 Able to stand with feet together for > 10 s, but only with sway
3 Able to stand for > 10 s without support in natural position, but not with feet together
4 Able to stand for > 10 s in natural position only with intermittent support
5 Able to stand > 10 s in natural position only with constant support of one arm
6 Unable to stand for > 10 s even with constant support of one arm

**Score** _____

### 3) Sitting

Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.

0 Normal, no difficulties sitting > 10 sec
1 Slight difficulties, intermittent sway
2 Constant sway, but able to sit > 10 s without support
3 Able to sit for > 10 s only with intermittent support
4 Unable to sit for > 10 s without continuous support

**Score** _____

### 4) Speech disturbance

Speech is assessed during normal conversation.

0 Normal
1 Suggestion of speech disturbance
2 Impaired speech, but easy to understand
3 Occasional words difficult to understand
4 Many words difficult to understand
5 Only single words understandable
6 Speech unintelligible / anarthria

**Score** _____

Rater: _____ date: _____ patient: _____

### 5) Finger chase

**Rated separately for each side**

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

- 0 No dysmetria
- 1 Dysmetria, under/ overshooting target <5 cm
- 2 Dysmetria, under/ overshooting target < 15 cm
- 3 Dysmetria, under/ overshooting target > 15 cm
- 4 Unable to perform 5 pointing movements

| Score | Right | Left |
|---|---|---|
| mean of both sides (R+L)/2 | | |

### 6) Nose-finger test

**Rated separately for each side**

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

- 0 No tremor
- 1 Tremor with an amplitude < 2 cm
- 2 Tremor with an amplitude < 5 cm
- 3 Tremor with an amplitude > 5 cm
- 4 Unable to perform 5 pointing movements

| Score | Right | Left |
|---|---|---|
| mean of both sides (R+L)/2 | | |

### 7) Fast alternating hand movements

**Rated separately for each side**

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

- 0 Normal, no irregularities (performs <10s)
- 1 Slightly irregular (performs <10s)
- 2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s
- 3 Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s
- 4 Unable to complete 10 cycles

| Score | Right | Left |
|---|---|---|
| mean of both sides (R+L)/2 | | |

### 8) Heel-shin slide

**Rated separately for each side**

Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

- 0 Normal
- 1 Slightly abnormal, contact to shin maintained
- 2 Clearly abnormal, goes off shin up to 3 times during 3 cycles
- 3 Severely abnormal, goes off shin 4 or more times during 3 cycles
- 4 Unable to perform the task

| Score | Right | Left |
|---|---|---|
| mean of both sides (R+L) / 2 | | |

Physiopedia contributors. Scale for the Assessment and Rating of Ataxia (SARA). Secondary Scale for the Assessment and Rating of Ataxia (SARA) 2020. https://www.physiopedia.com/index.php?title=Scale_for_the_Assessment_and_Rating_of_Ataxia_(SARA)&oldid=230367.

Appendix J: Modified Rankin Scale (mRS)

| Modified Rankin Scale (mRS) | Clinical Description |
|---|---|
| 0 | No symptoms. |
| 1 | No significant disability. Able to carry out all usual activities despite some symptoms. |
| 2 | Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities. |
| 3 | Moderate disability. Requires some help, but able to walk unassisted. |
| 4 | Moderately severe disability. Unable to attend to own bodily needs without assistance. Unable to walk unassisted. |
| 5 | Severe disability. Requires constant nursing care and attention, bedridden, incontinent. |
| 6 | Dead. |

Telischak NA, Wintermark M. Imaging predictors of procedural and clinical outcome in endovascular acute stroke therapy. Neurovascular Imaging 2015;**1**(1):4 doi: 10.1186/s40809-015-0004-z

Appendix K: Patient Fall Questionnaire

Patient No: _____
Date: _____
Training site: _____
Name of assessor: _____

What is a fall?
A fall is an event reported by the faller or a witness, resulting in a person inadvertently coming to rest on the ground or another lower level, with or without loss of consciousness or injury.

1. In the last 4 weeks, have you experienced a fall? Yes No
2. If you fell more than once in the last 4 weeks, how many times did you fall? _____

3. Did you lose consciousness during the event(s)? Yes No
4. Did your fall(s) result in injury requiring medical evaluation (e.g. fractures, concussion, bleeding in the brain)?
    a. If yes, please describe below:

Appendix L: Patient Baseline Characteristics

| Baseline Characteristics | RAS (n = 420) | Control (n = 420) |
|---|---|---|
| **Age (years)** | | |
| **Under 50** | Number, % | Number, % |
| **50-69** | Number, % | Number, % |
| **60-69** | Number, % | Number, % |
| **70-79** | Number, % | Number, % |
| **80 or greater** | Number, % | Number, % |
| **Sex** | | |
| **Male** | Number, % | Number, % |
| **Female** | Number, % | Number, % |
| **Education level** | Median years ± IQR* | Median years ± IQR |
| **Prior musical experience** | | |
| **Yes** | Number, % | Number, % |
| **No** | Number, % | Number, % |
| **MMSE* score** | Mean score ± SD* | Mean score ± SD |
| **Age at stroke onset** | | |
| **Under 50** | Number, % | Number, % |
| **50-69** | Number, % | Number, % |
| **60-69** | Number, % | Number, % |
| **70-79** | Number, % | Number, % |
| **80 or greater** | Number, % | Number, % |
| **Time since stroke onset** | | |
| **3-12 months** | Number, % | Number, % |
| **1-2 years** | Number, % | Number, % |
| **2 years or greater** | Number, % | Number, % |
| **Stroke type** | | |
| **Hemorrhagic** | Number, % | Number, % |
| **Ischemic** | Number, % | Number, % |
| **Vascular territory impacted** | | |
| **AICA*** | Number, % | Number, % |
| **PICA*** | Number, % | Number, % |
| **SCA*** | Number, % | Number, % |
| **2 vascular territories** | Number, % | Number, % |
| **3 or more vascular territories** | Number, % | Number, % |
| **Lesion size ($cm^2$)** | Mean size ± SD | Mean size ± SD |
| **Concurrent hemiparesis** | | |
| **Yes** | Number, % | Number, % |
| **No** | Number, % | Number, % |
| **Presence of complication** | | |
| **Edema** | Number, % | Number, % |
| **Herniation** | Number, % | Number, % |
| **Hydrocephalus** | Number, % | Number, % |
| **Brain stem involvement** | Number, % | Number, % |
| **Other** | Number, % | Number, % |
| **Surgical intervention** | | |
| **Yes** | Number, % | Number, % |
| **No** | Number, % | Number, % |
| **Length of inpatient stay (days)** | Mean time ± SD | Mean time ± SD |

*MMSE: mini-mental state examination, *AICA: anterior inferior cerebellar artery, *PICA: posterior inferior cerebellar artery, *SCA: superior cerebellar artery
*SD: standard deviation, *IQR: interquartile range

Appendix M: Rhythmic Auditory Stimulation (RAS) Treatment Protocol

Prior to training

Upon participant arrival, ensure that patients have proper training equipment (supportive footwear, non-restrictive clothing, etc.) and are ready to begin training.
An accompanying physiotherapist must be present for the duration of the training session.

Prior to the start of training, provide patients with an MP3 player and headphones for the delivery of personalized-cadence music at a comfortable volume.

Therapists must document patient training information, including discontinuation or pausing of gait trials for any reasons, adverse events, patient complaints, and clinical notes.

Training time: 30 minutes

5 minutes: Warm Up

- Instruct patients to begin listening to provided music at the beginning of training/warm-up
- Participants will be seated in a chair for the warm up
- Ask patients to tap their feet, nod their heads, and/or march in place in time with the cadence of the delivered beat

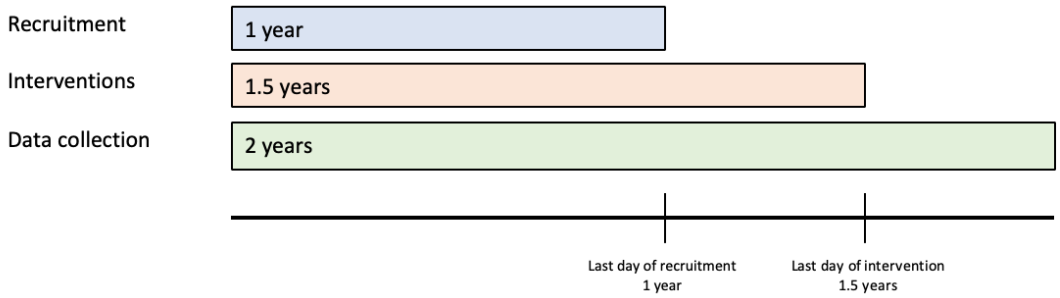
20 minutes: RAS training blocks (5, 2-minute trials) and breaks (5, 2-minute breaks)

- During delivery of RAS training, instruct patients to walk along a flat surface while matching his/her footfalls to the musical beat delivered through the MP3 player
    - Patients who feel unable to complete a trial due to fatigue, unsteadiness, dizziness, or other reason may discontinue the present gait trial. If comfortable and able, he/she may resume training as desired.
    - If patients are unable to match the delivered cadence, lower the delivered cadence to the most recent, highest, successfully-matched cadence.
- During breaks, patients should be asked to sit or stand comfortably

5 minutes: cool down

- Participants will be seated in a chair for the cool down
- Ask patients to tap their feet, nod their heads, and/or march in place in time with the cadence of the delivered beat
- Patients may continue to stretch if desired

Appendix N: Timeline for Patient Recruitment and Data Collection



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