Study of Postural Stability in Subjects with Myelopathy using a Portable Virtual Reality Balance Protocol

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Principal Investigator: Richard Servatius, PhD

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Abstract

Veterans are at heightened risk of developing cervical spondylotic myelopathy (CSM) from rigors of military service. Diagnosis of CSM involves a set of clinical findings and is confirmed by imaging the spine.

Gait impairment and disturbances of stance control are hallmarks of CSM and are a consequence of abnormalities in proprioception due to dorsal column tract damage of the spine. Currently, gait and balance deficits rely on clinical level assessments and judgement for detection. An objective measure of posturography has the benefit of: a) quantifying balance-related disability in CSM, b) facilitating structure-functional assessments in CSM, and c) quantifying the degree surgical interventions affect posturography and recovery of function in CSM.

Objective and sensitive means for assessing balance and posturography exist, but are not routinely incorporated in diagnosis or functional tracking of progress after interventions such as surgery. A barrier may be accessibility of posturography and ease of assessments. The Virtual Environment TBI Screen (VETS) was devised using Army Rapid Innovation Development funding to objectively assess balance and posturography in a cost effective, but sensitive manner. VETS involves virtual environments and computerized posturography and is proving to be a sensitive system facilitating diagnosis, treatment, and mitigation of balance dysfunction associated with mTBI.

Our working hypothesis is VETS testing will enhance clinical judgements regarding CSM. This study is designed to provide data critical to a more extensive program of research incorporating posturography into treatment and rehabilitation of CSM. First, a limited comparative study of standing balance will be conducted of 20 veterans being evaluated for cervical spine surgery to treat CSM and 20 otherwise healthy veterans. Second, posturography of the 20 veterans undergoing surgery to treat CSM will be tracked during their scheduled follow up visits to determine the degree VETS scores are affected by surgery and to track recovery from CSM.

List of Abbreviations

ALS	amyotrophic lateral sclerosis
ANOVA	analysis of variance
AUC	area under the curve
COP	center of pressure
CSM	cervical spondylotic myelopathy
CT	computed tomography
DYN	Dynamic
EC	Eyes Closed
EO	Eyes Open
mJOA	modified Japanese Orthopaedic Association scale
ML	medio-lateral
MMT	manual muscle test
MRI	magnetic resonance imaging
MRSR	Medical Research Surveillance Reports
MS	multiple sclerosis
MSE	multiscale entropy
mTBI	mild traumatic brain injury
NDI	Neck Disability Index
PTSD	posttraumatic stress disorder
ROC	receiver operating characteristic
SF-36	Short Form-36
SOT	Sensory Organization Test
SVAMC	Syracuse Veterans Affairs Medical Center
TBI	traumatic brain injury
VETS	Virtual Environment TBI Screen
VR	virtual reality
WBB	Wii balance board

Contents

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1.0 Study Personnel

Principal Investigator/Study Chair:

- Richard Servatius, PhD. SVAMC. Research Scientist, Director of the SMBI.

Co-Investigators:

- Steven Brose, DO. SVAMC. Chief of Spinal Cord Injury Unit.
- Aiga Rakhesh, MD. SVAMC. Neurologist, Spinal Cord Injury Unit
- Satyajit Marawar, MD. SVAMC. Chief of Spine Surgery.
- William Geoffrey Wright, PhD. SVAMC. WOC.

Coordinator:

- Amanda Haskell. SVAMC. WOC.
- Labeeby Servatius. SVAMC. WOC

2.0 Introduction

Cervical Spondylotic Myelopathy (CSM), also known as degenerative cervical myelopathy, encapsulates a cascade of events leading to significant degenerative changes in discs, formation of osteophytes, facet hypertrophy, calcification of the posterior longitudinal ligament and ligamentous flavum with resultant canal stenosis and segmental instability [1, 2]. Progressive impingement on tracts, nerve roots, and neurons may be confined to the cervical spinal cord or may be co-occurring in many locations throughout the spinal column.

In civilians, CSM reflects 'wear and tear' presenting generally in aging (> 50 year of age) and more often in males [3]. Incidence is estimated at 4.1/100,000 person years in North America [4]. Veterans are at greater risk for CSM owing to the rigors of military service (heavy axial loading, repeated vigorous activities, and direct trauma to the spine) [5, 6]. Although there are no agreed upon rates, degenerative disc disease is highly incident in military personnel and is responsible for lost duty time and medical evacuation from forward deployment [6]. Using Medical Research Surveillance Reports (MRSR) as a guide, incidence of cervical spondylosis is estimated at 150/100,000 person years for 2009 [7]. Although not specifically reported, incidence rates may be inferred to hold steady or slightly increase over the next surveillance period [8]. Tracking incidence of CSM from military service to veterans is difficult given the lack of an agreed upon criteria and absence of distinct pathognomonic findings [9]. However, it is reasonable to assume military experiences initiating degenerative processes would compound that of aging, which is the single most important risk factor in civilians [10].

Three areas are critical for early identification and management of CSM: detection and diagnosis [5], differential diagnosis [11], and functional tracking of signs and symptoms.

Detection and Diagnosis. Given the progressive nature of the disorder, timely identification and treatment is paramount [3]. Imaging of the cervical spine and notation of abnormalities alone is insufficient for diagnosis of CSM. Diagnosis of CSM involves a set of clinical findings which are confirmed by magnetic resonance imaging (MRI) and computerized tomography (CT) [12, 13]. The most common symptoms of CSM are: numb or clumsy hands, impaired gait, neck and leg stiffness, sensory disturbances in the arms or legs, atrophy of the hand musculature, and sensory loss. Signs of CSM are hyperreflexia, atrophy of intrinsic hand muscles, motor deficits, a broad-based, unstable gait, and bowel and bladder dysfunction. Both sets have considerable variability in presentation depending on cervical level and the degree and severity of impingement. Current tools to assess severity of functional impairment in CSM are the Nurick Scale [14, 15] for mobility, Neck Disability Index (NDI)[16] and the modified Japanese Orthopaedic Association (mJOA) scale [17], which provide a means for a standardized clinical scoring of dysfunction in broad strokes.

Differential Diagnosis. Differential diagnosis is challenging because there is a lack of a definitive finding or biomarker, and signs and symptoms overlap with a number of pathological sensorimotor conditions [5, 11]. The most common are multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), vitamin B12 deficiency and syringomyelia [11]. Differential diagnosis requires a host of invasive and noninvasive tests adding time, expense, and discomfort.

Treatment. Alleviation of impingement is typically surgical to decompress and stabilize the affected region [10]. There is considerable debate concerning the efficacy of surgical and nonsurgical interventions, the best type of surgical intervention, as well as the efficacy of combination approaches [3, 18-21]. With the available outcome measures (mJOA, NDI, Nurick), there is evidence of improvement after surgical intervention in moderate and severe cases of CSM, however, mild cases are less clear [10]. In this regard, the clinical scales suffer from a lack of sensitivity.

Critical Need. For all three areas – diagnosis, differential diagnosis, functional tracking in treatment – objective, empirical measures of dysfunction sensitive to severity of CSM have the potential to enhance rehabilitation of CSM in veterans.

Static balance and CSM. One area with a high potential to advance sensitivity, selectivity and gradations of CSM is a measure of static balance. Balance is the ability to maintain stable postural sway that does not exceed the limits of stability. Balance arises through the integration of sensory (somatosensory, vestibular, and visual inputs) and motor components (flexors, extensors). Sway, measured through center of pressure (COP), is a necessary component of posture as well as a well-established metric of postural control. Excessive sway is a sign of instability which may arise through sensory disturbances, motor dysfunction, or environmental perturbations.

Disturbances of postural control are hallmarks of CSM [22] and are a consequence of abnormalities in proprioception due to dorsal column or spinocerebellar tract damage of the spine [23] or postural commands to motor neurons [24, 25]. Those presenting to the emergency room for head trauma from falling were more likely to have CSM [26]. Similarly, those hospitalized for hip fracture were more likely to also have evidence of CSM than similarly aged individuals having elective hip arthroplasty [27]. Further, CSM increases the risk of subsequent injury after hip replacement [28]. Early detection could serve to decrease rates of injury and compound injury.

Nardone et al. [24] studied body sway of patients with severe CSM and cervical spondylosis without myelopathy using a force platform under conditions of eyes open or closed on a level firm surface compared to healthy controls. COP sway area was greater in both clinical groups under both eyes open and eyes closed conditions, suggesting disturbances of ascending proprioceptive input and impaired

descending motor control. Further, they found substantially greater COP sway area in CSM patients in the eyes closed than eyes open conditions, demonstrating the dependency on visual input for balance in CSM. Yoshikawa et al. [29] also observed that individuals with CSM presented larger COP sway than the less severe CSM, however, there was not supporting MRI or CT abnormalities presented to confirm CSM or its severity. Freppel et al. [30] found COP sway differences between patients with herniated disc and CSM suggesting that while symptom reporting was similar, posturography is sensitive to etiology (acute vs chronic degenerative disease). Thus, the assessment of static balance has considerable promise in providing an objective measure of dysfunction in CSM and contributing to differential diagnosis. Further, evaluating proprioception using posturography may also help to predict surgical outcomes. Takayama et al. observed that early proprioceptive recovery was associated with better functional outcome 2 years after surgery for cervical myelopathy [22]. Despite these promising findings, there has not been a study of posturography in veterans with CSM.

The Virtual Environment TBI Screen (VETS) is a new construct that has been validated for evaluating postural control processes. Building on established parameters, the VETS assesses posturography through easily accessible and relatively low cost technology. Currently, a Wii Balance Board (WBB – Nintendo, Kyoto, Japan) [31, 32] provides a surface for testing and stabilometers for transducing COP sway area. Virtual reality technology is used to simulate movement using a commercially available large screen television. There are three conditions (eyes open, eyes closed, and watching a dynamic visual scene) repeated on a firm surface or a foam surface. These 6 conditions allow for an assessment of generalized vs specific deficits in COP sway area considering proprioception (firm vs foam surface), dependence of visual input (eyes open vs eyes closed) and visuo-proprioceptive integration (static vs dynamic visual scene) (see Figure 1). The VETS device was specifically designed to be low cost (all components are commercial off-the-shelf) and easily assembled. The user interface was designed to be accessible to novice, but attentive providers. Algorithms are included to provide easily understandable measures among the six conditions. As a clinical device, further development is necessary.

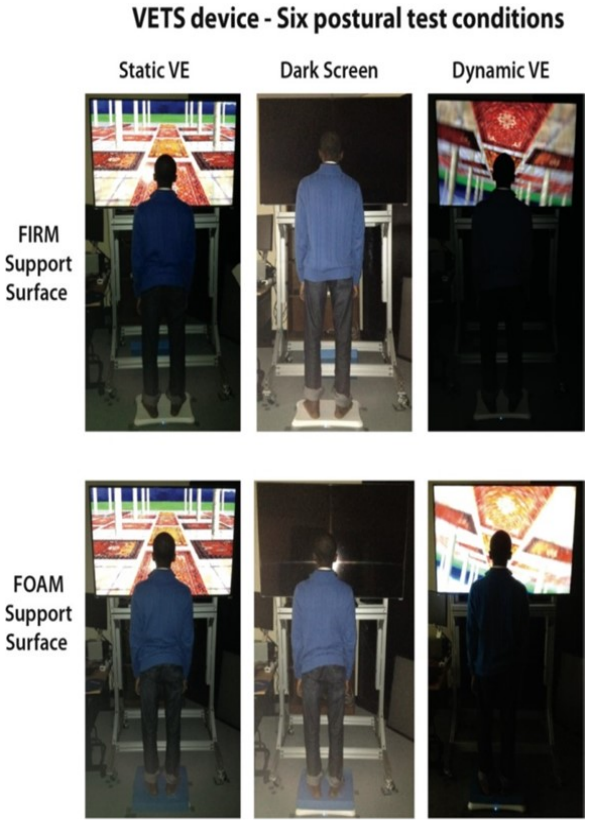

Figure 1. VETS - a VR-based balance assessment device tests six conditions. Top row shows the firm support conditions and the bottom row shows the unstable (foam) support conditions. From left to right, the three columns are eyes-open (EO) while viewing a static visual scene, eyes-closed (EC) in front of a dark screen, and EO viewing a dynamic rotating screen.

Although we have yet to examine posturography in veterans with CSM, Servatius and Wright have active collaborations to study posturography in active duty military (*Military Medicine* in press) and veterans. We are currently conducting a study of posturography at the Syracuse Veterans Affairs Medical Center (SVAMC) in veterans as a function of lifetime mild traumatic brain injury (mTBI) and posttraumatic stress disorder (PTSD). In the interim between initial submission and revision, two veterans with MS volunteered for the study. Although the study has a different focus, the data illustrates the sensitivity of the VETS to subtle differences in balance. No veteran in the study to date has registered a self-reported problem with balance. Figure 2 depicts COP sway for otherwise HEALTHY (N = 10), lifetime mTBI (N = 7) and MS (N = 2) veterans under the six conditions. In observing the otherwise HEALTHY veterans (open bars), one can see that the foam condition places a substantial burden on balance compared to firm conditions. Further, eyes closed conditions exacerbate COP sway area, especially on foam. One can also see that the ranges of COP sway area in normal

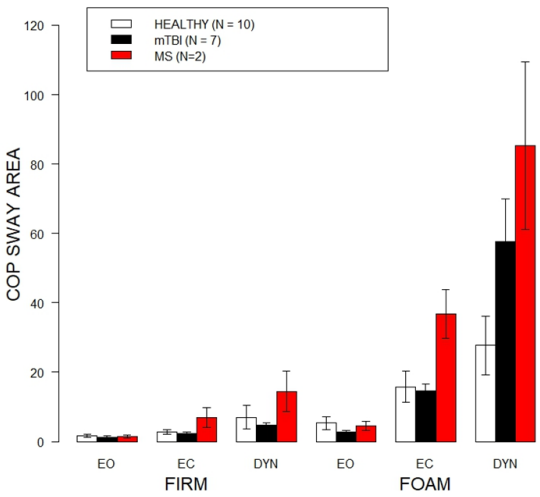

Figure 2. Comparison of VETS COP sway area in SVAMC veterans as a function of history of mTBI and MS. Legend is contained in the figure. The visual conditions were eyes open (EO), eyes closed (EC) and viewing a dynamically rotating science (DYN). These visual conditions were as on Firm and Foam surface. Veterans with lifetime history of mTBI exhibited greater COP sway area during the DYN-FOAM condition compared to HEALTHY veterans. MS veterans displayed greater COP sway area during the EC conditions, and the DYN-FOAM condition compared to HEALTHY veterans.

HEALTHY veterans provide substantial room to detect abnormalities. It is against this background that we will be assessing balance disturbances in CSM.

For the purposes of illustration we compared the two MS veterans to HEALTHY veterans with a 2 x 3 x 2 (Surface x Visual Condition x Clinical Group) mixed model analysis of variance (ANOVA) which yielded a significant triple interaction, $F(2,16) = 5.49$, $p = .014$. Specific comparisons between conditions showed the two eyes open conditions are similar to HEALTHY veterans (ps > .05) suggesting for these MS veterans postural control motor outputs are normal. Differences were apparent in the EC conditions suggesting visual input is necessary to maintain balance. Further, the DYN-FOAM condition was compromised in the two MS veterans (ps < .05), suggesting impaired ability to integrate visual, proprioceptive, and vestibular stimuli in MS. Comparison was also made between those with lifetime history of mTBI and HEALTHY veterans with a similar 2 x 3 x 2 (Surface x Visual Condition x Clinical Group) mixed model ANOVA. The triple interaction was significant, $F(1.176, 17.645) = 5.385$, $p = .028$ (Greenhouse-Geisser correction for violations of sphericity). Those with lifetime history of mTBI exhibit balance difficulties specifically on the DYN-FOAM condition ($p < .05$). For MS and lifetime mTBI, balance was compromised during the DYN-FOAM condition, which is designed to produce to roll vection [33], that is, perceived self-motion due to conflicting visual, proprioceptive and vestibular inputs.

The ongoing research in veterans demonstrates the utility of the six conditions comprising VETS to expose motor, proprioceptive, vestibular, and integrative sensory deficits. The combination of conditions in VETS provide a means to advance research in CSM beyond that already conducted in civilians to date.

Imposition of posturography is envisioned to aid in clinical assessment in CSM in three meaningful ways: a) assessment of CSM severity, especially in cases of 'mild' CSM, b) differentiating CSM from other entities, c) providing an objective target to assess treatments interventions and recovery. For differential diagnosis, the conditions potentially distinguished by posturography are trauma, ALS [34], MS (Figure 2), syringomyelia, myelitis, and vitamin B12 deficiency [35] (See Table 1).

Table 1. Sensory Motor Deficits and Expected Impact to Posturography with VETS

	Motor	Proprioception	VETS Conditions
CSM	?	?	EC, FOAM
Trauma	⬇⬇	⬇⬇	ALL
ALS	⬇⬇	Late Stages	ALL
MS	Late stages	⬇⬇	EC, DYN-FOAM
Syringomyelia	⬇⬇	Late Stages	ALL
Myelitis	varied	varied	
Vitamin B12 Deficiency	-	⬇	Normal EC

3.0 Objectives

AIM 1A: Determine whether and to what degree balance is altered in CSM. The degree of COP sway will be compared between CSM and controls in the six conditions comprising VETS testing.

> **Hypothesis 1**: Impaired proprioceptive transmission in CSM will result in poorer balance (larger COP sway area) during EC conditions (eliminating the ability to compensate with visual feedback) and FOAM (reducing the reliability of somatosensory feedback) conditions compared to healthy veterans.

AIM 1B: Determine whether VETS enhances sensitivity and selectivity in the diagnosis of CSM. Composite measures of balance will be related to clinical assessment tools and their relationship with MRI.

> **Hypothesis 2**: VETS will provide additional sensitivity and selectivity in identifying CSM compared to current clinical assessment tools.
> **Hypothesis 3**: The degree of COP sway area during EC and FOAM conditions is expected to directly relate to the degree of spinal cord compression quantified from MRI, leading to a more sensitive gradation in the severity of CSM.

AIM 2: Evaluate the VETS scores after surgery for CSM. The degree of COP sway area under the 6 conditions will be compared before surgery, 2 weeks, 6 weeks, and 6 months after surgery.

> **Hypothesis 4**: We expect surgery to reduce COP sway in EC conditions

4.0 Resources and Personnel

All research activities will be conducted at the Syracuse VA Medical Center, using equipment already owned by the PI. All research activities and data storage will take place in the D-wing of the SVAMC. Potentially eligible CSM patients will be identified by Drs. Casella, Brose, and Marawar during CSM surgery scheduling and referred to the study coordinator. Interested patients will be screened additionally and scheduled for an appointment if they are eligible. The study coordinator will consent the participants and obtain HIPAA authorization before collecting study data. Collecting study data will involve administering questionnaires and VETS testing. Drs. Casella and Marawar will complete the clinical scales being used in the study. Dr. Wright will process VETS data and Dr. Servatius will run all statistical analyses.

5.0 Study Procedures

5.1 Study Design

For AIM 1, a cross-sectional design that includes within-subjects (VETS conditions) and between-subjects (veteran groups) factors will be used to compare balance and posture in patients awaiting surgery for CSM ($n = 20$) to a cohort of age and gender-matched non-CSM controls ($n = 20$). The 20 veterans with CSM recruited for AIM 1 will also serve as the sample for AIM 2, which is a longitudinal assessment of balance following surgical intervention for CSM. The data generated from the proposed study will provide a base estimate of the variance in our veteran groups for use in the power calculation for a larger follow up study

Veteran volunteers (CSM and control) meeting eligibility criteria will complete one session of VETS balance testing. Those veterans awaiting surgery for CSM will be asked to return for three additional sessions of VETS at designated time points scheduled 2 weeks, 6 weeks, and 6 months post-surgery. For returning CSM veterans, self-report measures will be collected at each additional time point to compare objective (VETS) and subjective (scale measures) assessments of functional impairment related to CSM following surgery. None of the procedures involved in this research project will alter standard of care associated with CSM or the surgical treatment. "Each patient will be cleared by one of the study doctors (Dr. Marawar, Casella, or Brose) before participating in the post-surgery sessions. In the event that a patient is found to be physically incapable of safely participating in the first post-surgery session, they will not continue participation in the study until they are cleared by the study doctors. Thus, even if a patient is not cleared to participate in the two week post-surgery time point, they may be cleared to participate in the remaining two sessions (six weeks and six months post-surgery)."

Risks/Benefits of Participation

There are no risks associated with the questionnaires included in this study, as they ask only about physical symptoms and functioning associated with CSM. Although some emotional health questions will be included, they are not expected to be upsetting in any capacity.

The risks associated with VETS testing are minimal and are as follows:

- Discomfort from standing on the WBB or foam for a prolonged period of time
- Dizziness or disorientation when viewing the dynamic condition

These risks will be minimized by allowing participants to step off the WBB/foam between trials if the participant indicates any sign of discomfort. If a participant feels unable to continue with the testing, they will be allowed to cease participation at any time. All participants will be advised to step off the balance board if they feel too dizzy, to minimize fall risk. Additionally, the experimenter overseeing the VETS testing will be trained to spot participants to guard against falls.

We do not expect the inclusion of patients with both CSM and an additional diagnosis (i.e. neuropathy or lumbar spine disease) to alter the risk profile for the study, as each patient will be screened by study clinicians before being allowed to participate in the study. Any patient who is not found physically capable of completing the study assessments will not be informed of the study.

Participants will receive no direct benefit as a result of participating in this study. However, developing the VETS assessment as an objective marker of balance dysfunction in CSM will benefit veterans in the future who are being diagnosed, treated, and rehabilitated for CSM.

5.2 Recruitment Methods

Given the scope of the proposed study, a total sample size of 40 veterans is considered a realistic and achievable enrollment to generate pilot data. For AIM 1, a cross-sectional design that includes within-subjects (VETS conditions) and between-subjects (veteran groups) factors will be used to compare balance and posture in patients awaiting surgery for CSM ($n = 20$) to a cohort of age and gender-matched non-CSM controls ($n = 20$). The 20 veterans with CSM recruited for AIM 1 will also serve as the sample for AIM 2, which is a longitudinal assessment of balance following surgical intervention for CSM.

Drs. Casella, Brose and Marawar will identify potential participants for the CSM group by screening all CSM patients undergoing assessment and scheduling for surgical intervention. These potential participants will be referred to Dr. Servatius' study team, where a staff member will provide background information, additional pre-screening, and scheduling (if eligible and interested).

Healthy volunteers will be recruited using a poster/flyer within the SVAMC. Potentially interested participants will call the study staff, as prompted by the advertisement, and will undergo pre-screening and scheduling. A copy of this flyer may be found in the submission package. Healthy volunteers may also be recruited from the pool of participants who consented to future contact in the SMBI Data Repository. These individuals will be contacted by the research staff and will be asked if they are interested; the attached Telephone Script includes the language used for these participants.

For the cross-sectional arm of the study, veteran volunteers in the CSM and control conditions will be compensated $40 for their participation. Veteran volunteers in the CSM group will have the opportunity to earn an additional $40 for attending each of the three post-operative assessments, resulting in a maximum remuneration of $160. Participants will be paid in full for all sessions attended, even if they cease participation before fully completing a session. Payment will be sent in the form of a VA check to the address specified by the participant.

5.3 Informed Consent Procedures

Before the start of the testing session, the experimenter (the PI or a designated member of the research staff) will review the consent form with the participant and any study-related questions will be answered. This will take place in a private office. Participants will be encouraged to take their time and read the form carefully and in its entirety before they sign. Should the participant wish to take the consent form to review and think over, they will be permitted to do so. The participant's consent about his/her comprehension of the experiment and his/her willingness to participate will be obtained. The participant will also check a box indicating whether or not they consent to having their data stored in a research repository. Additionally, optional consent for recontacting will be requested. The participant will sign the form in front of the experimenter, indicating that they have read and understood all portions of the consent form, and the experimenter has answered any and all questions the participant had about the research of their participation. The same process will be followed for HIPAA authorization. The participant will be provided with a copy of the consent form and a copy of the signed HIPAA authorization form.

5.4 Inclusion/Exclusion Criteria

Inclusion criteria for the CSM group are:

- Symptoms of myelopathy in upper and lower extremities and stenosis of the cervical spine demonstrated by MRI or myelography
- Lower extremity muscle strength of 4 as quantified by manual muscle test (MMT) or above
- Ability to stand without support with eyes closed for 30 seconds or more.

Exclusion criteria for all study participants are:

- History of neurological disorder other than lumbar spine disease or peripheral neuropathy
- Inability to stand in an upright position with both feet together and eyes closed.

Veterans in the control group will be recruited via printed advertisement or through the SMBI Data Repository and age- and sex-matched with CSM veterans. Every effort will be made to ensure that the veteran participants enrolled in the proposed study are reflective of the VA population, with regard to sex and race/ethnicity. If any participant over the age of 89 happens to enroll, their exact age will be recorded as >89.

5.5 Study Evaluations

A. Materials

Scale Measures. Measures to be used in the proposed study include the modified Japanese Orthopaedic Association (mJOA) scale, the Nurick Scale, Neck Disability Index (NDI), and Short Form-36 (SF-36). The mJOA and Nurick Scale will be completed by one of the study team doctors during clinical visits, and the NDI and SF-36 will be completed by the participant. Participants will also fill out a demographics questionnaire once.

Modified Japanese Orthopaedic Association (mJOA) scale [17]. The mJOA is an instrument used to assess motor dysfunction of the upper and lower extremities, sensory loss of the upper extremity, and sphincter dysfunction. Motor dysfunction of the upper extremities is assessed on a 6-point Likert scale, with values ranging from 0 (inability to move hands) to 5 (no dysfunction). Motor dysfunction of the lower extremity is assessed on an 8-point Likert scale, with values ranging from 0 (complete loss of motor and sensory function) to 7 (no dysfunction). Sensory dysfunction of the upper extremities is assessed on a 4-point Likert scale, with values ranging from 0 (complete loss of hand sensation) to 3 (no sensory loss). Finally, sphincter dysfunction is assessed on a 4-point Likert scale, with values ranging from 0 (inability to micturate voluntarily) to 3 (normal micturation).

Nurick Scale [15]. The Nurick scale is a 6-grade ordinal scale assessing gait impairment, with grades ranging from 0 (signs and symptoms of root involvement but no evidence of spinal cord disease) to 5 (chair bound or bedridden).

Neck Disability Index (NDI) [16]. The NDI is a 10-item self-report questionnaire addressing function activities (personal care, lifting, reading, work, driving, sleeping, and recreation), pain intensity, concentration, and headache. For each item, patients make their ratings on a 6-point Likert scale with values 0 = no disability and 5 = complete disability. Summed scores for each category are multiplied by 2 to give a total NDI score ranging from 0-100.

Short Form-36 (SF-36) [37]. The SF-36 is a self-report general health survey that includes mental and physical component scores to measure functional status and overall quality of life. The instrument includes 8 scales: physical functioning, role limitations physical pain, bodily pain, general health perceptions, vitality, social functioning, role limitations, emotional health, and mental health.

Demographics: The demographics form will ask about basic information, including: age, sex, history of head injury, and current medications.

VETS. Postural stability will be assessed with the VETS system devised by Wright [31, 38-40]. All postural conditions are performed in a darkened room. The physical set-up has the front edge of the Wii balance board (WBB) placed at a distance of 40 cm from a 60” commercially-available flat screen television. This device employs a custom-designed software user interface that allows wireless Bluetooth collection of

center-of-pressure data at 100 Hz with high test-retest reliability and immediate display of results. Excellent concurrent validity was determined by comparing VETS with a research grade gold-standard NeuroCom, which revealed ICC > 0.90 (min: 0.901, max: 0.995, $p<0.01$).

The postural stability task will involve six conditions during which veterans are instructed to look straight ahead and maintain an upright stance as stably as possible (see Figure 2). Veterans are barefooted with feet comfortably placed ~25 cm apart. The six conditions are (1) Eyes Open (EO) Firm – eyes open with stable support surface (i.e. WBB) and static visual scene, (2) Eyes Closed (EC) Firm – eyes closed with stable support surface and dark screen, (3) Dynamic Scene (DYN) Firm – eyes open with a stable support surface while viewing a scene dynamically rotating in the roll (fronto-parallel) plane at 60 deg/s, (4) EO Foam - eyes open with unstable support (Airex foam pad placed on top of the WBB) and stable visual scene, (5) EC Foam – eyes closed with unstable support and dark screen, and (6) DYN Foam – eyes open with unstable support and rotating scene. Each condition lasts 30 secs and is repeated 3 times before progressing to the next condition. The conditions are tested in order 1-6, in a manner that emulates the validated Sensory Organization Test (SOT) protocol (Natus/Neurocom). For safety, an experimenter guards the veteran to protect against falls.

B. Procedure

Initial Testing Session: For all participants, the first session will involve obtaining informed consent and HIPAA authorization, completing self-report questionnaires, and a session of VETS testing. This initial session will last approximately 60 minutes. The informed consent procedure will follow the description outlined in section 5.3 and is expected to take around 15 minutes. Subsequently, the participant will fill out all listed self-report questionnaires, which will take about 15 minutes. Lastly, the participant will undergo one session of VETS testing, which will take about 20 minutes. VETS testing will follow the protocol outlined above in the "Materials" section. For CSM patients, one of the study doctors will fill out the clinical assessments during standard of care appointments throughout the study that correspond in time with the participant's research appointments.

All subsequent sessions (2, 3, & 4) will include CSM participants only, and will be conducted after surgical treatment.

Testing Session 2: Participants will be scheduled for the second testing session 2 weeks post-surgery. This session will include all self-report questionnaires except demographics and a session of VETS testing. It will last approximately 30-45 minutes.

Testing Session 3: Participants will be scheduled for the second testing session 6 weeks post-surgery. This session will include all self-report questionnaires except demographics and a session of VETS testing.

Testing Session 4: Participants will be scheduled for the second testing session 6 months post-surgery. This session will include all self-report questionnaires except demographics and a session of VETS testing.

5.6 Data Analysis

VETS data processing

The COP can analyzed by transforming of the time series into various traditional measures including sway area, sway velocity and AP and medio-lateral (ML) standard deviations. COP sway area is found using a principal component analysis, which approximates an ellipse around the x-y COP data using the first two eigenvectors. We will also assess COP velocity as a secondary dependent measure of balance dysfunction. COP velocity is calculated using the COP path length traveled in the x-y plane per time

epoch (0.01 sec). An instantaneous COP velocity is calculated for each sample and the average instantaneous COP velocity per trial. Multiscale entropy (MSE) is a nonlinear complexity measure of a time series over different temporal scales, which uses coarse-graining to average data points to generate a new time series [41]. Repeating structure within the point-to-point fluctuations of the postural signals over a range of time series can be sensitive to sensory reweighting during upright standing [42, 43]. MSE quantifies the physiological noise due to the various integrating processes, such that control and coordination of muscular contractions patterns employed during balance control can be systematically evaluated [44]. Our primary measure will be COP sway area, but all measures will be analyzed particularly to compare and identify the most sensitive and selective measure.

Statistical Analyses

All statistical analyses will be performed using IBM SPSS Statistics Version 24 and MedCalc. For descriptive purposes, continuous data will be summarized with the number of non-missing values, mean, and standard deviation, minimum, median, and maximum and categorical data will be summarized with the number of non-missing values and the numbers (frequencies) of values equal to each of the possible categories, unless stated otherwise. Univariate analyses will examine data distributions, potential outliers and missing data. All statistical tests will be two-sided with a significance level of alpha=0.05. Unless otherwise stated, no multiplicity adjustment will be applied and no missing values will be imputed.
For analysis of posturography data, each of the six VETS postural conditions (see Figure 2) will be tested three times for each participant from which an average is calculated for each condition. These within-subject, within-condition averages will be used in model building to assess between groups differences in balance (AIM 1a) and within-groups change in balance over time following surgical intervention (AIM 2).

For **AIM 1a**, mixed model ANOVA will be used to compare veteran group (CSM vs Control) and within-subject visual (EO, EC, and DYN) and surface conditions (FIRM and FOAM). Average COP sway, COP velocity, and MSE of COP sway velocity for each of the six VETS conditions will serve as dependent measures in separate models. Using Mauchly's tests, violations of sphericity will be detected, are corrected with Greenhouse-Geisser adjustments.

For **AIM 1b**, receiver operating characteristic (ROC) analyses will be conducted as a preliminary determination of sensitivity and specificity of VETS conditions to detect CSM. We will assess areas under the curve (AUC) and corresponding 95% confidence intervals, which will serve as indices of accuracy for CSM diagnosis. Using known groups (CSM and control veteran volunteers), we will compare AUC curves corresponding to 1) traditional diagnostic scale measures (e.g., mJOA scale, Nurick Scale, NDI, and SF-36), 2) VETS conditions, and 3) scale measures combined with VETS conditions. These analyses will serve as indicators for the degree the posturography, alone or in combination with scale measures, are sensitive and selective to CSM. An AUC = 0.50 will be considered chance level for correct classification into CSM and control groups. Differences in AUC for each of the three ROC curves will be accomplished using methods described by Delong et al [45].

For **AIM 2**, VETS data for CSM veterans will be assessed for changes in balance following surgical intervention. VETS dependent measures outlined above will be entered into repeated-measures ANOVA with time point (pre-surgery, 2 weeks, 6 weeks, and 6 months post-surgery) entered as an additional repeated measure. Using Mauchly's tests, violations of sphericity will be detected, are corrected with Greenhouse-Geisser adjustments.

5.7 Withdrawal of Subjects

Subjects will be told that they may withdraw from the study at any time. As soon as the subject notifies the PI or researcher that they wish to cease their participation in the study, any appointments will be canceled and the participant will be paid for any sessions partially or fully completed.

Participants may be withdrawn without their consent if the study is suspended during their participation or they suffer a health-related event within the time frame of their participation that precludes them from participating further, including complications from surgery.

6.0 Reporting

Adverse Event (AE): If a research participant exhibits acute discomfort as noted by the researcher during a testing session (e.g., expressing discomfort or overwhelming disorientation while standing on the VETS apparatus), they will be asked if they feel they are able to carry on with the session and offered a break. If they are unable to carry on, the PI will be informed immediately and the testing session will be terminated for the day.

Serious Adverse Event (SAE): An example of a SAE would be a participant suffering severe complications associated with the CSM surgical treatment. It is likely that such complications will occur only unrelatedly to any study activities—especially if a participant is prohibited from active participation while experiencing such complications. In the event that a participant has a strongly negative response to the surgery, the participant will not be scheduled for any post-surgical appointments.

An AE temporally related to participation in the study will be documented whether or not considered related to the test article or procedure. This definition includes current illnesses and injuries and exacerbations of preexisting conditions including changes to psychological state. AE will be kept in the subject tracking log and reported as a summary at continuing review. Expected adverse events which are not serious are reported on the Continuing Review Progress Report (CR). Any unanticipated adverse event related to application of tDCS will be reported to the IRB within 10 days, as per Federal Regulations Title 21 812.150 (1).

SAE, such as hospitalization for more than 24 hours, will be reported to the IRB within 5 days per SOP 151-17. This will be accomplished by submitting an adverse event report to the IRB.

7.0 Privacy and Confidentiality

Data Storage

All research data (physical and electronic) will be anonymized using identifiers supplied by the experimenter. In this study, each participant will be assigned a subject number (e.g., Subject 001), which will be used to link all data provided by the participant. There will be no direct correspondence between the participant's subject number and other personally identifying information, such as names or contact information, which could link them to the study or their data. Signed consent forms will be stored in a locked filing cabinet in room D311, which is located in a secured access research wing of the SVAMC. Only authorized study personnel will have access to these files.

De-identified electronic data will uploaded to a VAMC network computer for storage and data analysis purposes. Data will be stored in a secure, encrypted network subfolder (G:\SYR-MS\MS-SMBI). No study data will be stored on a computer hard drive. Only approved study personnel will have access to

electronic data. Raw numerical data from the VETS assessment containing no identifying information whatsoever will be shared offsite with Dr. Wright using VA Remote Access. This data is the output from our balance assessment, and contains nothing except numeric information reflecting the participant's standing balance pressure. No other information about the participant is contained in these files, although the files are named using the participant's unique study code. The paper study key will be maintained onsite and will never leave its locked file cabinet at the SVAMC. When study personnel are removed from the protocol, their access to the data will be terminated.

In the event that the security of VA research-related information (physical or electronic data) is compromised, either by unauthorized use, disclosure, transmission, removal, theft, loss, or destruction, the PI and authorized research staff will report to ACOS for Research, Privacy Officer, and Information Security Officer within 1 hour, as specified in Research & Development Policy 151-17.

Data Repository

During the consent process, the researcher will also obtain the participant's optional consent for storing data in a data repository. If the participant consents to data storage, their data will enter a data repository maintained at the Syracuse VA Medical Center by the PI and will not expire or be destroyed at the end of the current study. For all participants who do not consent to having their data entered into the data repository, their study records will be destroyed within 6 years of the end of the study, as per RCS 10-1.

Participants will agree to the data repository both in the consent form and in the HIPAA authorization form. Data entered into the data repository will be maintained in the manner detailed in the IRB protocol submitted for the data repository itself. Only authorized study personnel will have access to the data repository, and access will be terminated immediately upon an individual's removal from the protocol.

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