The Motor Control Consequences of Excessive Physical Therapist Support in Individuals with Stroke (NCT04856527)

University of Cincinnati IRB Protocol 2020-1072

Most recent IRB approval: 2021-10-07

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Study Protocol

Participants

Twenty participants aged 21-85 years[1] previously diagnosed with stroke (>1-month prior to enrollment to ensure medical neurologic stability) will participate in Experiment 1 (10 participants in experimental group, 10 participants in control group). Participants will be randomly assigned to a group. Participants must demonstrate independence or modified independence during ambulation (defined as the ability to ambulate with no physical assistance and use an assistive device as needed). Participants must score 0-3 on the Modified Rankin Scale (de Haan et al., 1995; Rankin, 1957), which indicates complete independence to moderate disability but able to walk without assistance. Participants must be able to maintain standing balance for >2 minutes with no physical support and maintain grasp of a handheld object with at least one hand. Participants are permitted to be active in programs of physical therapy or occupational therapy at the time of enrollment. All gender identities and all races/ethnicities will be eligible for participation.

Participants with stroke will be excluded due to limited language/cognitive abilities, deafness, blindness, or serious motor impairment that outright prevents performance of the experimental tasks (e.g., severe upper or lower extremity spasticity). Participants will be excluded if they are pregnant. Participants will also be excluded if they experience pain with weightbearing >4/10. Participants will complete the Mini Mental State Exam (Folstein et al., 1975) prior to study start to ensure cognitive capacity to engage in and consent to the study. Participants will be excluded if they have any other medical condition that would preclude the valid administration of the study measures, specifically seizure disorders, additional neurologic conditions beyond stroke, or significant musculoskeletal conditions (e.g., lower limb amputation).

Participants with stroke will be recruited from a large outpatient neurologic rehabilitation clinic part of a larger, nonprofit medical center in the midwestern United States. Further, participants will also be recruited from the UC Stroke Recovery Registry. This registry contains over 750 persons with chronic stroke who have expressed a desire to be involved in stroke-related research at UC. The registry is shared among researchers in the College of Allied Health Sciences, the College of Medicine, and the College of Nursing. All participants will receive compensation for time and travel.

Materials and Apparatus

Participants will be placed in a virtual environment created with the Unity game engine (Unity Technologies, San Francisco, CA) while donning a VIVE virtual reality (VR) headset (HTC Corporation, Bellevue, WA). Postural sway will be measured using a force platform (AMTI AccuSway, Advanced Mechanical Technology, Watertown, MA). For the

[1] This is the age range *approved* by the IRB. Age range will be narrowed once it is ascertained what range is available for recruitment. Most likely, participants will be > 60 years. However, if a large sample of younger adults < 45 years is available, that will become an eligibility criterion, and the study will be conducted with young adults with stroke.

transfer task, light finger force production will be measured with a 1500 g force transducer (Measurement Specialties, Inc., Dayton, OH). A visual display created in Processing (v.3.5.4) will communicate level of light force production to participants. The virtual environment will be rendered at a rate of 90 Hz. Postural sway data and light force production will be sampled continuously at a rate of 150 Hz.

Experiment 1: Postural Support and Task Learning

Pre-Test
In Experiment 1, participants will be required to learn an upper limb precision aiming task while receiving postural support (i.e., balance facilitation) or no postural support. Baseline performance will be measured prior to a practice period. For this pre-test, participants will stand on the force platform for 30 s trials. Within the VR environment, participants will see an anteriorly placed circular target and will be instructed to maintain the position of a virtual laser pointer in the target via a handheld device in the dominant hand (or both the non-paretic and paretic hands for participants with stroke) with the upper limb held at the side. The target will change color to communicate task accuracy to participants: When the virtual laser is correctly positioned within the target, the target will be blue, but misaiming will turn the target red, indicating the need to correct the laser position. Participants will only visualize the laser and target in VR; there will not be a virtual representation of the upper limb. Participants with stroke will complete two 30 s pre-test trials with each hand (paretic and non-paretic). Postural sway and projection of the laser will be measured and recorded.

Transfer Task
As therapists expect that training in a set of tasks might benefit performance of other similar but untrained tasks (i.e., transfer), a task to assess transfer will also be implemented. This task will be completed both prior to the practice period (to obtain a baseline level of performance for comparison after practice) and after the practice period. In the transfer task, participants will attempt to use their dominant hand (or both non-paretic hand and paretic hand for participants with stroke) second digit to produce a specified level of light touch force (0.5-1 N to prevent physical stabilization) on the force transducer. Like the laser pointer task, this task requires integration of postural control with precision manual performance (e.g., Riley et al., 1999b). Participants will receive visual feedback regarding their level of light touch force production on a visual display. A vertical bar will appear on the screen. The bar will increase in vertical size with increased force production and decrease in size with less force production. The bar will change color to reflect the level of force production. When the bar is blue, the desired level of force production has been achieved. When the bar is red, the participant needs to alter the level of force production. A horizontal line will also indicate target force production. Participants will complete two 30 s trials of the transfer task. Participants with stroke will complete the transfer trials with each limb.

Practice
Following the pre-test and baseline transfer task, participants will engage in 10, 1 min practice blocks in which they are to practice the laser task with the target positioned

laterally. This lateral placement of the target during the practice period (as opposed to the anterior position of the pre-test) will prevent one group of participants from practicing under the exact conditions of the pre-test, which could bias the results. This will also allow for an assessment of differences in sway variability that may facilitate performance at post-test, thus providing insights about generalizability. The control group will receive no physical support to maintain balance. The experimental group will receive physical support (whether physical support is warranted or not) to minimize postural sway fluctuations. Participants with stroke will use the paretic hand. Participants will be outfitted with a gait belt, and physical support will be provided through the use of the gait belt and other traditional physical therapy guarding techniques (O’Sullivan et al., 2019). Thus, participants in this group will not be required to coordinate posture and task performance because postural stabilization will be provided externally through physical support. Postural sway and virtual laser position will be synchronously recorded during the practice period. Participants will rest for a self-selected period between each trial.

Immediate Post-Test and Retention

Participants will complete a post-test following the same procedure as the pre-test (i.e., target task). The post-test will also involve the previously described transfer task. Participants will complete two 30 s trials of each task (target/force production). Participants with stroke will complete the trials with each limb. Task and condition will be randomized. No physical support will be provided in the post-test.

Design

To evaluate the learning effect in participants with stroke, the two groups (experimental, control), two hands (paretic, non-paretic), and two test conditions (pre-test, immediate post-test) will result in a 2 × 2 × 2 mixed design for Experiment 1. Participants with stroke will complete 2 trials of each test condition per limb for a total of 8 test trials per participant. To evaluate the role of therapist support during practice, each participant will complete 10 practice trials. Participants will complete 4 trials (2 trials per limb) of the transfer task before and after practice for a total of 8 trials.

Proposed Data Analysis

All data processing and analyses will be completed using custom R scripts (v.4.0.3). All postural sway data (i.e., center of pressure—COP) will be filtered through a 4^{th}-order lowpass zero-lag Butterworth filter with a cut-off frequency of 6 Hz prior to analysis.

Recurrence Quantification Analysis (RQA)

RQA (Webber & Zbilut, 2005) will be used to assess the regularity of postural sway. RQA quantifies the patterning, non-stationarity, and complexity of biological time series through the analysis of local recurrences in a reconstructed phase space (Riley et al., 1999a). Recurrence plots (RPs) provide a visualization of patterns of recurrence, where a single point on the RP indicates a recurrence and a line indicates continuing recurrence (Coco & Dale, 2014). A variety of metrics are used to quantify these patterns. Percent determinism (%DET) is the percentage of recurrent points which fall on diagonal lines and reflects how often the system repeats the same sequence of points. Thus, higher %DET is indicative of a system with more regularity. Maximum line length (MAXLINE) is the length of the longest diagonal line segment on the RP, indicating the maximum duration of time that the system is revisiting an area of reconstructed phase space. Mean line length (MEANLINE) is the average length of diagonal line segments on the RP, indicating the average duration of time that the system is revisiting an area of phase space. In the context of the current study, reduced task-sensitive adjustments (i.e., modulation in task relevant direction) in %DET, MAXLINE, and MEANLINE of postural sway (hypothesized to exist following constraining posture/task) would indicate a more regular postural control system—one that is prone to repeating the same behaviors. RQA metrics will be calculated separately for each plane.

Sample Entropy (SampEn)
SampEn (Richman, Lake, & Moorman, 2004) will be used to evaluate changes in the predictability of postural sway as a convergent measure to complement RQA. SampEn evaluates the predictability of the next state of a system, given what is known about the current state of a system (Yentes, 2016). SampEn has been widely used to assess the regularity of postural control across a variety of task conditions and populations (e.g., Schmit et al., 2016). SampEn will be calculated separately for each plane.

Traditional Analyses
Due to the wide use of COP path length and standard deviation (SD) of COP in the literature, these metrics will also be measured to further quantify changes in postural sway. These metrics are also important for assessing the distribution of sway in each plane as a function of task demand. COP path length refers to the amount of displacement of the location of the (resultant) vertical ground reaction force vector. Increased COP path length is often interpreted as reduced stability. SD of the COP is the typical method used to quantify the variability in COP trajectories. Higher values for SD of the COP indicate increased variability. COP path length is a bi-planar measure whereas SD of the COP will be calculated separately for each plane.

Supra-Postural Task Performance
Root mean square (RMS) deviation of the observed supra-postural task performance from the expected values will be used to determine the accuracy of supra-postural task performance. For Experiments 1 and 2, this will be defined as the deviation of the laser position from the target. For the transfer task, this will be defined as the deviation from the target range of light touch force production.

Statistical Analysis
To characterize learning of the practiced supra-postural laser/target task and the associated postural sway patterns, trials (error score and postural sway metrics) for both experiments will be submitted to mixed-effects models. Group (experimental, control), test condition (pre-test, immediate post-test), limb (paretic, non-paretic), and their interactions will be entered as fixed effects, and participant will be entered as a random effect. To assess performance (error score and postural sway metrics) during the practice period, trial number (1-10), group (experimental, control), and their interaction will be

entered as fixed effects and participant will be a random effect. For the transfer task (error score and postural sway metrics), group (experimental, control), test condition (pre-test, immediate post-test), limb (paretic, non-paretic), and their interactions will be entered as fixed effects, and participant will be entered as a random effect. A backward stepwise approach will be used for model building. Simple effects and pairwise comparisons will be used to follow up on significant interactions.

Relevant References

Balasubramaniam, R., Riley, M. A., & Turvey, M. T. (2000). Specificity of postural sway to the demands of a precision task. *Gait & Posture, 11*(1), 12-24.

Coco, M. I., & Dale, R. (2014). Cross-recurrence quantification analysis of categorical and continuous time series: An R package. *Frontiers in Psychology*, *5*, *510*, 1-14.

de Haan, R., Limburg, M., Bossuyt, P., Van der Meulen, J., & Aaronson, N. (1995). The clinical meaning of Rankin 'handicap' grades after stroke. *Stroke, 26*(11), 2027-2030.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198.

McCamley, J. & Harrison, S. J. (2016). Introduction. In N. Stergiou (Ed.), *Nonlinear analysis for human variability* (pp. 1-28). Boca Raton, FL: CRC Press.

O'Sullivan, S. B., & Schmitz T. J. (2007). *Physical rehabilitation* (5th ed.). Philadelphia, PA: FA Davis.

O'Sullivan, S. B., Schmitz, T. J., & Fulk, G. (2019). *Physical rehabilitation* (6th ed.). Philadelphia, PA: FA Davis.

Rankin, J. (1957). Cerebral vascular accidents in patients over the age of 60: II. Prognosis. *Scottish Medical Journal, 2*(5), 200-215.

Richman, J. S., Lake, D. E., & Moorman, J. R. (2004). Sample entropy. In *Methods in Enzymology* (Vol. 384, pp. 172-184). https://doi.org/10.1016/S0076-6879(04)84011-4.

Riley, M.A., Balasubramaniam, R., & Turvey, M.T. (1999a). Recurrence quantification analysis of postural fluctuations*. Gait & Posture, 9*(1), 65-78

Riley, M. A., Stoffregen, T. A., Grocki, M. J., & Turvey, M. T. (1999b). Postural stabilization for the control of touching. *Human Movement Science, 18*(6), 795-817.

Webber, C. L., & Zbilut, J. P. (2005). Recurrence quantification analysis of nonlinear dynamical systems. In M. A. Riley & G. C. Van Orden (Eds.), *Tutorials in contemporary nonlinear methods for the behavioral sciences* (pp. 26-94). Retrieved from https://www.nsf.gov/ pubs/2005/nsf05057/nmbs/nmbs.pdf.

World Health Organization. (2001). *International classification of functioning, disability and health: ICF.* Geneva: World Health Organization.

Yentes, J. M. (2016). Entropy. In N. Stergiou (Ed.), *Nonlinear analysis for human variability* (pp. 173-260). Boca Raton, FL: CRC Press.