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Application Title: Efficacy of Metacognitive-Strategy Training to Improve Activity Performance and Reduce Motor Impairment in Sub-Acute Stroke

Protocol

1. Abstract

The long-term goal of this research is to improve activity performance and reduce motor impairment in individuals with stroke. There are two primary gaps in current stroke rehabilitation practice that must be addressed to achieve this goal: (1) current impairment-based approaches (e.g. motor) are not improving meaningful activity performance; and (2) current stroke rehabilitation interventions are often not designed to be clinically feasible and are rarely implemented into practice. The overall hypothesis of this proposal is that a clinically-feasible, activity-based intervention, metacognitive strategy training (MCST), will produce a significant improvement on objective and subjective measures of activity performance and motor function in comparison to a usual care occupational therapy (OT) group. These gains will transfer and generalize to untrained tasks in novel environments. The specific aims of this project are: (1) to evaluate the efficacy of MCST to improve subjective and objective activity performance in individuals with subacute stroke; and (2) to evaluate the efficacy of MCST to improve motor function in individuals with subacute stroke. Participants with subacute stroke living in the community with self-identified activity performance goals and hemiparesis will be recruited through a local stroke registry (n = 108). Those individuals who meet inclusion and exclusion criteria will be randomized to either a MCST group or to a usual care occupational therapy group. Both groups will receive ten, 45 minute sessions of treatment. Treatment outcomes will be assessed baseline, post-intervention, and at three-months post-intervention. Treatment efficacy outcomes will be analyzed with an intent-to-treat model with an analysis of covariance (ANCOVA). Potential covariates will include age, stroke severity, degree of cognitive impairment, and degree of motor impairment. Independent samples t-test and chi-square test will be used to ensure successful randomization and balance between groups. Group differences at baseline that are statistically significant will also be considered as covariates in the analysis. Post-hoc tests will be employed as appropriate. Significance levels, effect sizes, and confidence intervals will be reported. Completion of this study is likely to result in an efficacious, clinically feasible intervention to improve activity performance and reduce motor deficits in individuals with stroke that can be feasibly implemented into current systems of care. The proposed study and anticipated outcomes are consistent with the research priority of the National Center for Medical Rehabilitation Research (NCMRR), which is to focus on identifying, preventing, and treating key secondary conditions that are associated with physical impairments and disabilities, including stroke.

2. Objectives

The goal of this proposed project is to evaluate the efficacy of a clinically-feasible metacognitive strategy training (MCST) intervention, the Cognitive Orientation to daily Occupational Performance (CO-OP) approach, to improve activity performance and reduce stroke impairment for individuals with sub-acute stroke.

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

Contemporary stroke rehabilitation focuses on remediation of post-stroke impairments with a false assumption that reduction in impairments will automatically lead to improvements in activity performance. Specifically, stroke rehabilitation is focused primarily on the use of task-specific training (TST), which recent research has found to yield negligible improvement in upper extremity motor function often consistent with or less than control conditions.1,2 These protocols are time intensive and often do not lead to transfer of training effects to improvement in activity performance. This is a common issue that has been evidenced in longitudinal studies of individuals with stroke; over half of stroke survivors continue to be dependent on others for the most basic of life activities after rehabilitation.3 Decreases in activity performance further contribute to lower life satisfaction, quality of life, and participation in daily life.3-5

Recent evidence highlights two primary issues in stroke rehabilitation. 1) Interventions are needed that directly target activity performance. Gains in upper extremity function, even using the most contemporary approaches, are not translating to meaningful gains in activity performance. 2) Interventions need to be clinically feasible for future implementation. In recent stroke rehabilitation clinical trials, participants received an average of over 30 hours of therapy in only one treatment modality.1,2 Individuals in stroke rehabilitation receive a median of only 6 outpatient visits across *all* health care specialties combined (OT, PT, SLP, physiatrist).6

Metacognitive strategy training (MCST), specifically the Cognitive Orientation to daily Occupational
Performance (CO-OP) approach, is a potential solution to address both of these gaps. CO-OP is a performance-based, problem-solving approach that enables participants to improve task performance through cognitive strategy use.7 In our exploratory clinical trial for individuals with sub-acute stroke (n=26) we compared ten, 45-minute sessions of MCST (CO-OP) with dose-matched outpatient usual care outpatient occupational therapy (OT).7,8 The MCST (CO-OP) group demonstrated a large effect over usual care on objective measures of trained functional activities (d=1.6) and untrained functional activities (d = 1.1).7 The MCST group also demonstrated a moderate effect over usual care outpatient OT on improving motor function (r = 0.3)8

4. **Study Procedures**

   a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).
   b. Study duration and number of study visits required of research participants.
   c. Blinding, including justification for blinding or not blinding the trial, if applicable.
   d. Justification of why participants will not receive routine care or will have current therapy stopped.
   e. Justification for inclusion of a placebo or non-treatment group.
   f. Definition of treatment failure or participant removal criteria.
   g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

a. We will use a single-blind, parallel, randomized clinical trial design. The raters who will complete all the outcome assessments will be blinded. Participants will be asked prescreening questions over the phone to determine eligibility. Following baseline testing (T1), subjects will be randomized to either receive ten 45 minute sessions of metacognitive-strategy training (the Cognitive Orientation to daily Occupational Performance approach) (CO-OP) or dose-matched usual care outpatient occupational therapy. Each group will receive a total of ten 45-minute

treatment sessions, once a week. After completion of 10 intervention sessions, subjects will complete a post-intervention assessment (T2). A follow-up assessment will be conducted at three months post-intervention assessment (T3).

Name	Time Frame	Brief Description
Canadian Occupational Performance Measure (COPM)	T1, T2, T3	The COPM is a semi-structured interview guide for establishing a subject's activity performance levels within self-care, leisure, and productivity. The subject will set a minimum of 5 activity goals, providng a self-rating of 1-10
Performance Quality Rating Scale (PQRS)	T1, T2, T3	The PQRS is an observational, objective method of scoring subject activity performance of goals set via the COPM. A blind, trained rater external to the research study team will view video recordings of each subject performing goals. Each goal is rated on a scale of 1 (no activity criteria were met) to 10 (all activity criteria were met). The final score will be an average of all 5 goals.
National Institutes of Health (NIH) Toolbox Cognition Battery	T1, T2, T3	The NIHTB-CB is a collection of 7 computer-based measures assessing episodic memory, executive function and attention, working memory, language, and processing speed. As a whole, the NIH-CB is a brief assessment of fluid intelligence including problem-solving, judgment, thinking, and memory. In the present study, the fluid cognition composite T-score representing executive function will be used as an outcome measure.
Upper Extremity Fugl-Meyer	T1, T2, T3	The Fugl-Meyer is a well-established measure of upper extremity motor performance in individuals with post-stroke hemiparesis. Each item is scored either a 0 (cannot perform), 1 (performs partially), or 2 (performs fully) with a maximum score of 66.

		In the present study, the upper extremity scaled scored will be utilized.
Patient Health Questionnaire (PHQ-9)	T1, T2, T3	The PHQ-9 is a self-report measure of depressive symptoms. The subject identifies how often over the previous 2 weeks they have experienced 9 depressive symptoms. The total score reflects the severity of depressive symptoms. A score of 21 or greater indicates severe depressive symptoms. This variable will be treated as a covariate.
Montreal Cognitive Assessment (MoCA)	T1	The MoCA is a brief screener for dementia symptoms. Sixteen items are used to assess short-term memory, language, orientation, and visuospatial abilities. Within the present study, a previously established cut-off score of <23 will be indicative of cognitive impairment.
Stroke Impact Scale (SIS)	T1, T2, T3	The SIS is a self-report measure of stroke recovery. Specifically, the measure assesses physical, cognitive, psychosocial, community mobility, and general activity performance on a 5 point Likert scale. There is an additional item for overall recovery rated on a scale of 0 (no recovery) to 100 (full recovery).
Life Space Questionnaire	T1, T2, T3	Self-reported measure of community mobility and social participation. It is comprised of 9 yes/no questions related to places visited in the previous three days. Total score will be used in analysis.

b. Involvement in this study will consist of 3 assessment visits and 10 treatment visits, one treatment per week. The study will last for approximately 24 weeks with a total time commitment between 13-14 hours as follows:

- baseline assessment (2 hours),
- CO-OP (ten, 45 minute sessions) or
- usual care outpatient occupational therapy (ten, 45 minute sessions),
- post-intervention assessment (2 hours), and
- follow-up assessment (2 hours).

c. All raters who complete outcome assessments will be blinded to prevent biased assessment of outcomes. It is impractical to blind treating therapists, participants, and key personnel for a behavioral study of this nature.
d. This study does not request individuals to stop their routine care or current therapy. However, if a person is actively receiving rehabilitation for their upper extremity, they are not eligible to participate in this study as to avoid compromising the outcome measurement results.
e. It is important to include a usual care Occupation therapy group, so as to evaluate if MCST is more effective at improving activity performance and reducing motor impairment.
f. Participants will be removed from the study if they fail to meet to eligibility criteria or if the participant fails to attend one assessment or two treatment visits and research staff are not able to reach the participant after several attempts.
g. Participation in this study will not affect the participant's health care in any way, regardless if their participation in the study ends prematurely.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:
- less than 6 months post-stroke
- adults age 50-85
- completed inpatient rehabilitation services (if recommended)
- living in the community with or without caregiver support (i.e., not living in a skilled nursing facility)
- ability to read, write, and speak English
- self-identified activity performance goals per the Canadian Occupational Performance Measure (COPM)
- upper extremity hemiparesis as indicated by a score of 1-3 on the NIHSS motor arm score

Exclusion Criteria:
- inability to provide informed consent
- severe depressive symptoms as indicated by a score >21 on the Patient Health Questionnaire (PHQ-9)
- dementia symptoms as indicated by a score of <23 on the Montreal Cognitive Assessment (MoCA)
- additional neurological diagnoses identified by medical chart review (e.g., brain malignancy)
- moderate or severe aphasia as indicated by a National Institutes of Health Stroke Scale (NIHSS) aphasia score of 2 or higher
- no voluntary movement in affected upper extremity as indicated by a score of 4 on the NIHSS motor arm score
- anosognosia as indicated by an inability to identify activity performance problems on the COPM or PQRS
- any other condition not otherwise specified that the PI determines would render participation in this study as unsafe
- currently receiving outpatient rehabilitation for their upper extremity

6. Drugs/ Substances/ Devices

N/A

7. Study Analysis Plan

a. Primary outcome variable.
b. Secondary outcome variables.
c. Statistical plan including sample size justification and interim data analysis.
d. Early stopping rules.

a. The primary outcome variables will be the COPM, PQRS, and Upper Extremity Fugl-Meyer.

b. The secondary outcome variables will be the NIH Toolbox, PHQ-9, MoCA, SIS, and Life Space Questionnaire.

c. All data will be cleaned and checked for accuracy. Data accuracy will be evaluated using a double-data entry procedure (see *Data Safety and Monitoring Plan*). As a randomized design we expect the treatment groups to be well balanced. There is always the potential for differential attrition to result in treatment groups that are somewhat imbalanced with respect to potential covariates predictive of the outcomes (see Table 3). Prior to the initial analysis we will examine differences in potential covariates and those that exhibit statistically significant and clinically meaningful differences between groups will be included as covariates in the analysis. The primary analysis for Aims 1 & 2 will be a two-factor (Group, Time) analysis of variance (or covariance) with time the repeated factor. Following a statistically significant time by group interaction effect, contrasts will be constructed to test for group differences by time point and estimate within-group change from baseline at each time point. Estimation will be via maximum likelihood methods that do not require complete data for each participant but do assume the drop out mechanism is non-informative. The primary analysis follows the intention-to-treat principal, but should the groups differ with respect to drop-out or compliance we will treat "dose" as a covariate for a secondary analysis of each aim.

d. This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

8. Risks

There are no expected risks from participation in this study. This expectation is based on the nature of the behavioral study but also on substantial preliminary data across three clinical trials the PI has conducted investigating this specific intervention and/or similar behavioral interventions. The risks associated with participation in this study are no greater than what the subjects may encounter in everyday life. The following risks are considered rare possible risks from participation in this study.

1. Breach of confidentiality: With any research study involving human subjects, there is a possible risk of a breach of confidentiality where identifiable health information related to the subjects is inadvertently made available to individuals beyond the research team.

2. There is the risk that confidentially will be initially broken if during the PHQ-9 interview, the participant indicates they have considered the following over the last two weeks, "Thoughts that you would be better off dead, or of hurting yourself in some way," their treating physician will be notified. The interviewer will also give the participant mental health resources, including a psychiatrist and psychologist contact information. If someone states they have intentions of

hurting themselves we will encourage them to go to the emergency room for immediate support and care. If necessary, security will be called to escort them to the emergency room.

3. Psychological distress: In rare circumstances, subjects may experience psychological distress while discussing changes in their abilities following stroke.

4. Physical injury: Subjects will perform their chosen activity-related goals with trained rehabilitation personnel. Some of these goals involve physical activity (e.g., cooking), in which the subject could sustain a physical injury, such as a cut on the hand.

5. There is the low risk that some questions during testing may make the participant feel bored or frustrated.

9. Benefits

The subject may potentially experience benefit from participating in either the CO-OP intervention or from usual care outpatient occupational therapy by performing the activities addressed in treatment better and/or experiencing less stroke-related impairment (e.g., motor impairment). The potential benefits definitely outweigh the risks. The risks of participating in this study are minimal and considered rare. The potential benefits of this study could also extend to the subjects' family members and friends through decreases in caretaker burden as a result of potential gains in function on the part of the subject.

We hope that in the future other people might benefit from this study because it will help health care professionals determine the best intervention and assessment methods to use for persons with stroke in order to improve their ability to participate in everyday life activities and/or reduce stroke-related impairment, e.g., motor impairment. This study can help address this very important clinical issue.

10. Payment and Remuneration

Each subject will be paid $50 following the each of the 3 assessments, for a total of $150.00. The payments will be in the form of a University issued check mailed to participants' homes within 2 to 3 weeks of each assessment completion date.

11. Costs

There will be no cost to the participants.

12. Data and Safety Monitoring Plan

The research coordinator will oversee the review of all data collection forms on an ongoing basis for data completeness and accuracy, as well as protocol compliance. All data files completed during the specified time period will be reviewed. The study coordinator will assign a rater to review each file who was not the person who collected the data. The reviewer will complete an audit sheet to review the completeness and accuracy of each data file. Data verification will be completed on all outcome data by double data entry. All data will be entered into a separate electronic database. The research coordinator will cross-check the two data files and resolve any discrepancies. The results of the data verification will be reported on the audit form. All audit forms will be reviewed by the PI and further training of blind raters will occur if consistent errors are noted. Any protocol violations will be reported to the University of Missouri Health Sciences IRB. Intervention fidelity and protocol adherence will be reviewed by the PI, with support from the CO-OP Academy, who is a certified trainer in the CO-OP approach. The CO-OP Academy has developed a CO-OP Fidelity Checklist that is used to monitor fidelity of the CO-OP. This checklist will be completed by reviewing video recordings of intervention sessions and therapists must maintain an overall score of 80% to be compliant with

the intervention. Any items missed on the checklist will be reviewed with the therapist during the next weekly meeting following the audit. Failure to maintain an 80% on any fidelity check will require individual instruction. For every participant, a minimum of two sessions are recorded: (1) one from sessions 2-5; and (2) one from sessions 6-9. Additional sessions may be recorded and reviewed at the PIs discretion, if therapists are consistently scoring at or below the 80% threshold.

Subject Accrual and Compliance

Subject accrual (including compliance with protocol enrollment criteria), status of all enrolled subjects, as of date of reporting, and outcome data accuracy (double-data entry) will be reviewed quarterly by a blind rater (confirmation by researcher coordinator and PI). Adherence data regarding study visits and intervention will be reviewed quarterly by PI. Treatment fidelity will be reviewed quarterly by PI (with CO-OP Academy). Adverse Events and rates will be reviewed quarterly by PI and medical monitor. Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur quarterly during the 3.5 year recruitment phase to ensure that: (1) a sufficient number of participants are being enrolled; (2) participants are meeting eligibility criteria; and (3) the targeted ethnic diversity goals outlined in the grant proposal are being met (see Inclusion of Women, Minorities, and Children).

Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

Safety Review Plan

Study progress and safety will be reviewed quarterly. Annual progress reports, including patient recruitment, retention/attrition, and AEs, will be provided to the University of Missouri Health Sciences IRB. The annual report will include a list and summary of AEs. In addition, the annual report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The annual report will be provided to the sponsoring IC as part of the RPPR. The IRB and other applicable recipients will review progress of this study on an annual basis.

13. References

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4. Bergström AL, von Koch L, Andersson M, Tham K, Eriksson G. Participation in everyday life and life satisfaction in persons with stroke and their caregivers 3–6 months after onset. *Journal of rehabilitation medicine.* 2015;47(6):508-515.

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6. Chan L, Wang H, Terdiman J, et al. Disparities in outpatient and home health service utilization following stroke: results of a 9-year cohort study in Northern California. *PM&R.* 2009;1(11):997-1003.

7. McEwen S, Polatajko H, Baum C, et al. Combined cognitive-strategy and task-specific training improve transfer to untrained activities in subacute stroke: an exploratory randomized controlled trial. *Neurorehabilitation and neural repair.* 2015;29(6):526-536.

8. Wolf TJ, Polatajko H, Baum C, et al. Combined cognitive-strategy and task-specific training affects cognition and upper-extremity function in subacute stroke: an exploratory randomized controlled trial. *American Journal of Occupational Therapy.* 2016;70(2):7002290010p7002290011-7002290010p7002290010.