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The Prognostic Utility of EEG in Post-Stroke Upper Extremity Motor Recovery

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THE PROGNOSTIC UTILITY OF EEG IN POST-STROKE UPPER EXTREMITY MOTOR RECOVERY

BY

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A doctoral project submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree Doctor of Health Administration in the College of Health Professions

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Chapter 1: Introduction

1.1 Background

Stroke Prevalence: Stroke is a leading cause of long-term disability that affects nearly 800,000 people in the United States each year.[1] Of those affected by stroke, 50-80% experience upper extremity (UE) impairment that reduces the individuals' ability to perform daily tasks inedependently.[2-4] For 40-50% of these individuals, the UE impairment will be chronic and persist for 6 months or longer post-stroke.[4,5] However, the extent of recovery of the paretic UE varies widely among chronic stroke survivors.

Need for Prognosis: Here, rehabilitation prognosis pertains to the extent of motor function recovered by the paretic UE (i.e., arm and hand) following therapy. Uncertain prognosis for UE motor recovery presents a hurdle in developing personalized UE rehabilitation treatment plans for individual patients. Improved prognosis may guide therapists to set realistic therapy goals related to UE function and choose the maximally efficient course of treatment for their patients. For example, for patients predicted to have less UE recovery, therapists may focus on caregiver training, instruction of compensatory UE techniques, and implementation of adaptive equipment. For patients predicted to have greater UE recovery, therapists may focus on incorporating the paretic UE in high-level instrumental activities of daily living, such as meal preparation.

Conventional Predictors: Conventional predictors of post-stroke UE recovery include initial clinical motor score (e.g. Fugl-Meyer Upper Extremity Assessment), age, sex, presence of a motor evoked potential, and presence of a somatosensory evoked potential (SEP).[6] Meta-analysis shows that time since stroke and lesion volume do not predict recovery, while the initial motor score is the most significant predictor.[6] However, the effect sizes for such findings have been shown to be inflated, meaning the strength of the association between initial clinical motor scores and recovery may be overly optimistic.[7,8]

Solution: UE motor recovery may be better predicted by initial neural function (i.e., the integrity of neural function within the residual neural circuits post-stroke prior to therapy).[9] because initial neural function facilitates neuroplastic changes necessary for motor recovery[10] to occur. In particular, electroencephalography (EEG) may be used to assess neural function and predict post-stroke UE motor recovery. While other instruments such as magnetic resonance imaging (MRI)[11-15] and transcranial magnetic stimulation (TMS)[16] may be used to assess initial neural function, EEG offers the following compelling advantages.

Advantages of EEG: The primary advantage of EEG is that it measures multiple aspects to provide a complete picture of neural function for UE movement (Figure 1), whereas TMS is limited to measures of corticospinal[17] tract integrity. Specifically, the neural circuit for UE function may be assessed using the following 4 EEG measures: (1) the ascending pathway integrity is assessed using SEP,[18] which is a direct measure of the sensory signal from the UE arriving at the primary sensory cortex in the brain,[19] (2) communication within the brain to plan/process/control UE movement is assessed via cortico-cortical connectivity,[20] which is a measure of coherence in electrical activity between brain regions[21] involved in the sensory and motor control of the UE,[20,22-28] (3) the motor command for UE movement is assessed via spectral power change,[20] which is a measure of neuronal firing change within the primary motor cortex during UE movement,[20] and (4) the connection between the brain and hand muscle for generating movement is assessed via cortico-muscular connectivity, which is coherence in electrical activity between the primary motor cortex and the hand muscle.[29]

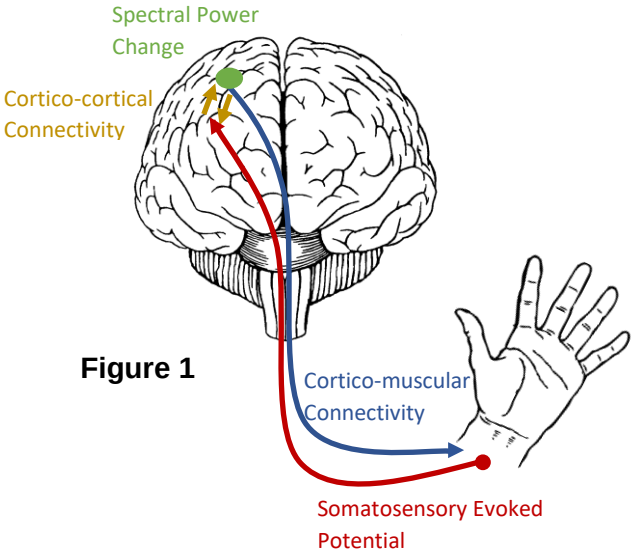

Figure 1

Additional advantages of EEG are that it provides a direct measure of functional electrical activity of neuronal assembles in the brain that facilitate neuroplastic changes necessary for motor recovery to occur,[10] as opposed to structural MRI or indirect hemodynamic response in the brain measured with fMRI. While EEG has poor spatial resolution compared to MRI, it has superior temporal resolution, capturing millisecond changes in neural activity relevant for function.[30] Furthermore, EEG has no contraindications, while approximately 20% of stroke survivors cannot undergo MRI or TMS due to contraindications such as metal implants in the body.[31] In addition, EEG is less expensive, can be performed at bedside unlike MRI, and is already used in clinical practice in the acute inpatient hospital setting.

1.2 Objective

The objective of this study is to determine the prognostic utility of EEG in post-stroke UE motor recovery. Improved prognosis of post-stroke UE motor recovery is expected to direct UE rehabilitation goal setting and treatment planning resulting in the most effective course of therapy for individual patients. Improved prognosis is also expected to enhance therapists' confidence in treating patients.[9]

1.3 Research Question

1. Can EEG improve prognosis of post-stroke upper extremity (UE) motor recovery?

1.4 Specific Aims

Aim 1: To determine the prognostic utility of EEG in stroke recovery via a systematic review and meta-analysis.

Hypothesis 1: EEG predicts post-stroke recovery outcomes.

Aim 2: To establish feasibility of using EEG to predict post-stroke UE motor recovery from an UE therapy program.

Hypothesis 2: It is feasible to collect EEG and assess post-stroke UE motor recovery during an UE therapy program.

Aim 3: To determine if EEG predicts post-stroke UE motor recovery following an UE therapy program.

Hypothesis 3: EEG predicts post-stroke UE motor recovery following an UE therapy program.

Chapter 2: Aim 1

Manuscript 1:

The Prognostic Utility of EEG in Stroke Recovery: A Systematic Review and Meta-Analysis

The Prognostic Utility of EEG in Stroke Recovery: A Systematic Review and Meta-Analysis

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Abstract

Background: Improved ability to predict patient recovery would guide post-stroke care by helping clinicians personalize treatment and maximize outcomes. Electroencephalography (EEG) provides a direct measure of the functional neuroelectric activity in the brain that forms the basis for neuroplasticity and recovery, and thus may increase our prognostic ability.

Objective: To examine evidence for the prognostic utility of EEG in stroke recovery in a systematic review/meta-analysis.

Methods: Peer-reviewed journal articles that examined the relationship between EEG and subsequent clinical outcome(s) in stroke were searched using electronic databases. Two independent researchers extracted data for synthesis. Linear meta-regressions were performed across subsets of papers with common outcome measures to quantify the association between EEG and outcome.

Results: 56 papers were included. Association between EEG and clinical outcomes was seen not only early post-stroke, but also more than 6 months post-stroke. The most studied prognostic potential of EEG was in predicting independence in the standard acute stroke care setting. The meta-analysis showed that EEG was associated with subsequent clinical outcomes measured by the Modified Rankin Scale, National Institutes of Health Stroke Scale, and Fugl-Meyer Upper Extremity Assessment ($r=0.74$, 0.59, and 0.56 from 7, 9, and 7 papers, respectively). EEG improved prognostic abilities beyond prediction afforded by standard clinical assessments. However, the EEG variables examined were highly variable across studies, and did not converge.

Conclusions: EEG shows potential to predict post-stroke recovery outcomes. However, evidence is largely explorative, primarily due to the lack of a definitive set of EEG measures to be used for prognosis.

Keywords: Stroke, EEG, rehabilitation, prognosis, meta-analysis

1. Introduction

Stroke is a leading cause of long-term disability in the United States.[1,2] Since stroke is heterogeneous, functional ability and treatment response vary greatly among stroke survivors.[3] Currently, due to poor prognostic abilities, clinicians experience difficulty developing personalized treatment plans that maximize patient outcomes. Improved prognostic ability would direct treatment planning and provide individual patients with the maximally efficient course of treatment. Specifically, physicians may utilize patients' recovery prognosis to determine the most appropriate discharge setting. Once patients are referred to rehabilitation, therapists may utilize patients' recovery prognosis to set appropriate rehabilitation goals and administer individualized therapy. For example, for patients predicted to require a moderate level of assistance, therapists may focus on caregiver training, teach compensatory techniques, and introduce adaptive equipment. Alternatively, for patients with a prognosis of independence, therapists may focus on restoring function in daily activities, with goals targeted at improving strength and functional ability. Overall, improved prognostic ability can save both the patient and healthcare system time and resources while maximizing outcomes.

To aid with prognosis, many studies have investigated potential predictors of post-stroke outcome including initial clinical assessment, age, sex, time since stroke, and lesion volume. Meta-analysis shows that the initial motor score is the most significant predictor, while time since stroke, age, sex, and lesion volume do not predict recovery.[4] The prognostic utility of the initial clinical score for recovery, however, has recently been shown to be spurious.[5,6] Specifically, the effect sizes reported for such findings are likely inflated, meaning the strength of the association between initial scores and recovery may be overly optimistic.[5]

Outcome may be better predicted by neural function (i.e., the integrity of neural function within the residual neural circuits post-stroke).[7] In particular, electroencephalography (EEG) may be used to assess neural function and predict post-stroke recovery. While other instruments such as magnetic resonance imaging (MRI)[8-12] and transcranial magnetic stimulation (TMS)[13] are also used to assess residual neural resources, EEG offers several compelling advantages. First, EEG provides a measure of *direct*, *functional* electrical activity of neuronal assembles in the brain that facilitate neuroplastic changes necessary for motor recovery[14] to occur, as opposed to structural MRI or indirect hemodynamic response in the brain measured with fMRI.[15] While EEG has poor spatial resolution compared to MRI, it has superior temporal resolution, capturing millisecond changes in neural activity relevant for function.[15] EEG also offers measurement of multiple aspects, including integrity of the afferent sensory tract[16,17] and the corticospinal tract,[18] as well as local[19] and network[20] electrical activity in the cortex, whereas TMS is limited to measures of corticospinal[21] and corticobulbar[22] tract integrity. Furthermore, EEG has no contraindications, while approximately 20% of stroke survivors cannot undergo MRI or TMS due to contraindications such as metal implants in the body.[23] In addition, EEG costs less than MRI, can be performed at bedside unlike MRI, and continuous EEG monitoring is already used in clinical practice for some stroke patients in the acute hospital setting.

Overall, the objective of this study was to perform a systematic review and meta-analysis to determine the prognostic utility of EEG for post-stroke outcome. Qualitative synthesis of evidence exists in a recent review.[24] To further this knowledge, the present paper provides a *quantitative* synthesis of evidence with a meta-analysis. In addition, the previous review[24] examined 25 papers exclusive to acute/subacute stroke (<6 months post-stroke) in 4 outcome domains (i.e., mortality, function, epilepsy, cognition). In contrast, the present paper synthesized

56 papers pertaining to both acute/subacute and chronic stroke (≥6 months post-stroke) in 9 outcome domains (i.e., independence, stroke severity, upper extremity, speech, whole body sensorimotor, balance/gait, cognition, mortality, level of consciousness). It is important to consider prognosis in the chronic phase given accumulating evidence showing that neuroplasticity and subsequent recovery extends beyond 1-year post-stroke.[25] Through comprehensive qualitative and quantitative synthesis of the literature, we aim to provide an overview of the prognostic potential of EEG in predicting post-stroke outcomes.

2. Methods

2.1 Search Strategy

We followed the PRISMA guidelines for systematic reviews and meta-analyses[26] to examine the prognostic utility of EEG in stroke outcome. A literature search was conducted in PubMed (Medline), Scopus, and CINAHL databases. The search terms used were stroke and electroencephalography or EEG. We developed our search strategy based on consultation with a medical librarian and consideration of the literature. The search included papers published between 1965 and 2019 and was last searched on January 10, 2019.

2.2 Inclusion and Exclusion Criteria

2.2.1 Systematic Review

I. Publication

   a. Inclusion:

      i. Peer-reviewed journal paper.

      ii. Written in English.

II. Study design

a. Inclusion:

i. Papers that acquired EEG for clinical and/or research purposes.

ii. Papers that examined the relationship between baseline EEG and subsequent stroke related clinical outcome measures.

iii. Papers that reported statistical analysis results for prognosis and/or provided data sufficient for independent statistical analysis for prognosis.

b. Exclusion:

i. Meta analyses, reviews, clinical guidelines, case studies, commentaries, and trial protocols.

ii. Papers that did not measure EEG.

iii. Papers that did not include a clinical outcome measure.

III. Participant characteristics

a. Inclusion:

i. Study participants had a stroke(s) of any type.

2.2.2 Meta-Analysis

I. Outcome measure

a. Inclusion:

i. Outcome measure common in at least five papers.

b. Exclusion:

i. Papers that utilized a modified outcome measure (e.g., dichotomization, proportion, partial items).

II. Statistics

a. Exclusion:

i. Papers did not provide relevant statistics or data needed to calculate relevant statistics, or authors did not provide data upon request.

2.3 Screening

Papers were screened by the primary and the senior author independently. Papers were initially screened based on the title and abstract. For papers that met the inclusion criteria based on the title and abstract, full-text papers were obtained and a subsequent screening was performed to determine if the inclusion criteria were met. The senior author completed 30% of the initial abstract screening and 32% of the full-text screening. In cases of discrepancy, resolution was found by a joint re-review of the paper.

2.4 Analysis for Systematic Review

Study characteristics were extracted from the selected papers, including patient characteristics, time since stroke, medical treatment, EEG protocol, EEG variable, outcomes, and findings. In addition, methodological quality of the papers was determined according to the modified Downs and Black Checklist.[27-30] The modified version of the checklist[27-30] was used due to the limited number of experimental intervention studies included in this review. Two independent raters determined quality of the papers included in the meta-analysis and one of the raters determined the quality of all remaining papers included in the systematic review.

Findings were classified as positive or negative based on the following criteria. (1) Findings with $p<0.05$ were counted as positive and findings with $p>0.05$ were considered as negative for regressions, correlations, odds ratios, t-tests, and ANOVAs. (2) In cases of multiple regression and/or ANOVA with other predictors (e.g., initial clinical score), the finding was considered as positive if EEG contributed to the statistical model. (3) If a p-value was not provided, correlation coefficients or predictive values ≥ 0.6 were considered as positive and findings with <0.6 were considered as negative.[31] Papers were then classified as "positive" if they presented only positive findings for EEG prognosis, "negative" if they presented only negative findings, and "mixed" if they presented both positive and negative findings.

The results of papers were qualitatively examined against study characteristics including sample size, time post-stroke at EEG and at outcome, EEG variable, number of EEG electrodes, outcome domains, and quality score, to investigate the association between study characteristics and prognostic results.

2.5 Meta-Analysis Method

For each paper, we extracted a correlation coefficient between baseline EEG and a subsequent outcome measure. When an odds ratio was provided instead of a correlation, a transformation to the scale of a correlation coefficient Yule's Q[32] was applied. Two papers[33,34] that examined the same sample of subjects were treated as a single paper in the analysis. Six papers[33-38] reported EEG and/or outcome measure scores at two or more timepoints. Therefore, we included data at each timepoint. For 13 papers that did not provide the data needed to calculate relevant

statistics, the authors were contacted via email. One author responded and provided additional data from which correlation was calculated and included in the meta-analysis.

The correlation coefficient of each paper was then transformed using Fisher transformation for normal distribution.[39] To estimate an average association between EEG and clinical outcome, a linear meta-regression was performed for each outcome, adjusting for sample size and study quality. Weighted sample size (=√[n/total n of included papers]) and weighted quality scores (=√[score/max possible score]) were used in the analysis. To account for multiple EEG and/or outcome measure times within a single paper, study ID was included in the analysis as a random effect for all models. Time of EEG, outcome time, time between EEG and outcome, and time post-stroke were adjusted for but did not significantly contribute to any of the regression models and were removed.

3. Results

3.1 Systematic Review

Search results

Results of the literature search and screening are summarized using the PRISMA 2009 flow diagram in Figure 1. A total of 56 papers met inclusion criteria and were synthesized for the systematic review. These 56 papers included a total of 2,947 participants' data, with the average age of participants in each paper ranging from 45 to 75 years. The majority of the papers were published in the last decade (Figure 2A). Of 56, 28 papers reported mixed results (i.e., both positive and negative), 24 only positive, and 4 only negative (Figure 2A). The detailed study information including characteristics of patients, EEG, outcome measures, and quality scores of each paper can be found in supplement A.

Time since stroke

The majority of the papers assessed EEG for prognosis within one-month post-stroke (Figure 2B). Across all times post stroke, the majority of studies found positive or mixed results for the predictive ability of EEG. Interestingly, negative findings were not associated with later time post stroke, and the proportion of papers with positive findings did not decrease with increasing time post stroke (Figure 2B). This observation remained despite the fact that time post stroke stretched to 1-8 years post stroke in the chronic papers.

Type of stroke

Of the 56 papers, 37 included only ischemic stroke and 19[36,40-57] included both ischemic and hemorrhagic stroke. However, of those that included both types of stroke, no papers compared prognosis between ischemic and hemorrhagic stroke. Thus, direct comparisons between stroke type could not be made. However, 2 papers compared ischemic stroke subtypes.[58,59] Specifically, one study found that for posterior circulation syndrome, EEG within 3 days post stroke was associated with 1-week stroke severity measured by the National Institutes of Health Stroke Scale (NIHSS) but not independence measured by the Modified Rankin Scale (MRS), while the opposite was seen for lacuna syndrome.[58] The other study found that EEG within a week post stroke was predictive of 1-year MRS for both cortical and lacunar syndrome.[59]

Treatment

Of 50 papers with mean EEG time $\leq$2 months post stroke, 48 papers followed standard care, which encompassed inpatient hospitalization and/or inpatient rehabilitation therapy. The other 2 papers used a standardized treatment in which all patients received the same dose of a particular treatment (auditory discrimination training[60], mechanical endovascular therapy[61]) (Figure 3). The other 6 papers with mean EEG time ranging 3 months to 8 years post stroke used

a standardized upper extremity treatment including standardized manual motor rehabilitation[40,41,43,62] visuomotor tracking training[42], and robot assisted therapy.[44]

EEG protocol

EEG was obtained for both clinical[51,63-66] and research[33-38,40-50,52-62,67-89] purposes. Of 50 papers with mean EEG time ≤2 months post stroke, 36 papers obtained resting EEG, while 14 papers obtained EEG response to stimuli, the majority being electrical nerve stimulation in 9 papers (Figure 3). The other 6 papers with mean EEG time >2 months post stroke obtained EEG during resting (n=3) and upper limb movement (n=3).

EEG variables & Outcome

EEG variables used varied considerably across papers. Thus, EEG variables were grouped into power, event related potential, epileptiform, connectivity, and dipole-based EEG variable types (Figure 3). Outcome measures also varied considerably across papers, and were, therefore, grouped into outcome domains of independence, stroke severity, upper extremity, speech, (whole body) sensorimotor, balance/gait, cognition, mortality, and level of consciousness (Figure 3).

The positive, mixed, and negative findings were spread across EEG variable types and outcome domains (Figure 4). Nearly two-thirds of papers assessed power (e.g., brain wave oscillation symmetry, delta to alpha power ratio, peak frequency). As such, power had the most positive and most negative findings. The majority of papers (n=53 papers) examined a single EEG variable type. Thus, direct comparison of prognostic potential across multiple EEG variable types is limited.

The most assessed outcome domain was independence (n=20 papers, e.g., MRS), followed by stroke severity (n=17 papers, e.g., NIHSS). Independence also had the largest number of papers with positive findings (Figure 4).

Quality score, sample size, EEG to outcome time, number of EEG electrodes

The quality score ranged from 7 to 14, with a mean+SD=11±2 points, out of 16 points. Twenty six papers were found be of "good" quality (≥71%), 25 "fair" (54-70%), and 5 "poor" (≤53%).[27,90] The poor quality was due to absence of variance estimates and/or actual probability values (e.g., reporting <0.05 rather than exact p-values) and absence of description or adjustment for confounding variables, such as age and initial clinical score of patients. Poor quality was associated with earlier publication time, as 4 of the 5 poor quality papers were published between 1982 and 1994. Detailed quality score information including the number of points received on each item of the checklist and the total score for each paper can be found in supplement B.

Sample size ranged from 6[52] to 351[73] participants (median=36). EEG to outcome time ranged from 4 days[66] to 3 years[84] (median=2 months). The number of electrodes used ranged from 1[48] to 256,[41,42] with 19 being the most used.[33,34,60,65,66,71,75,76,79-81,85]

The prognosis results of each paper are plotted against quality score, sample size, EEG to outcome time, and number of EEG electrodes in Figure 5. Papers with negative findings appear to have a combination of a (i) long time period between EEG and outcome measure (e.g., 2-3 years), (ii) low quality score, (iii) low sample size, and (iv) low number of EEG electrodes (Figure 5).

Prognosis beyond conventional predictors

A total of 21 papers examined if EEG enhanced prognostic ability more than prognosis by the conventional predictor of baseline clinical score. Fourteen papers found positive results. Specifically, the examined EEG variable(s) significantly explained variance in outcome after controlling for initial clinical score in 6 papers.[48,54,62,64,80,85] In 3 papers, EEG further separated patients with good or poor prognosis after the consideration of the initial clinical score.[38,49,59] In 5 papers, EEG correlated with outcome while initial clinical score did not.[41,47,65,78,86] Mixed results were found in 6 papers, where EEG enhanced prognostic ability of conventional predictors only for some EEG variables,[76,81] EEG time,[33] subgroup,[71] outcome domain,[72] and analysis method.[58] A negative result was found in 1 paper, in which only cerebral blood flow, not initial clinical score or EEG, predicted 3-year outcome.[84]

Explorative investigation

It was evident during the review that the majority of papers involved exploratory investigation. Specifically, 25 papers reported prognostic results for each of multiple EEG variables (e.g., simple correlations), including not only different EEG variable types (e.g., power, connectivity), but also multiple frequency bands (e.g., delta, theta, alpha, beta, gamma), multiple brain regions (e.g., ipsilesional, contralesional), multiple parameters (e.g., amplitude, latency, relative vs. absolute power, power ratio, dipole x, y, and z coordinates) and different tasks during EEG (e.g., eyes open vs. close, movement preparation vs. execution). In addition, 15 papers used an approach to statistically select a subset of multiple EEG variables for best prognostic results (e.g., stepwise regressions). Further, many papers examined prognostic results for multiple outcome times (n=6) and multiple outcome domains (n=11).

3.2 Meta-Analysis

Search results

Results of the meta-analysis screening are summarized using the PRISMA 2009 flow diagram in Figure 1. Of the 56 papers included in the systematic review, 21 papers met the inclusion criteria and were synthesized for the meta-analysis. Quality scores ranged from 9 to 14, with mean+SD=12±2 out of 16 points. Twelve papers were found be of "good" quality (≥71%) and 9 "fair" (54-70%) quality.[27,90] The outcome measures examined were: (1) MRS[91] which measures the degree of disability/dependence in daily activities, (2) NIHSS[92] which measures stroke severity, and (3) Fugl-Meyer Upper Extremity Assessment (FMUE)[93] which measures upper extremity motor impairment.

Correlation between EEG and MRS

Seven papers utilized MRS as the outcome measure. These papers presented 13 EEG and MRS correlations (Figure 6A) in a total of 186 participants. All papers assessed the EEG variable type of power. Linear meta-regression of the correlation between baseline EEG and subsequent MRS demonstrated a strong[31] adjusted effect of 0.74 (95% CI: 0.66-0.80).

Correlation between EEG and NIHSS

Nine papers utilized NIHSS as the outcome measure. These papers presented 12 EEG and NIHSS correlations (Figure 6B) in a total of 295 participants. They included multiple EEG variable types, including power and connectivity. Linear meta-regression of the correlation between baseline EEG and subsequent NIHSS demonstrated a moderate[31] adjusted effect of 0.59 (95% CI: 0.50-0.66).

Correlation between EEG and FMUE

Seven papers utilized FMUE as the outcome measure. These papers presented 9 EEG and FMUE correlations (Figure 6C) in a total of 187 participants. They included multiple EEG variable types, including power, connectivity, and event related potential. Linear meta-regression of the correlation between baseline EEG and subsequent FMUE demonstrated a moderate[31] adjusted effect of 0.56 (95% CI: 0.45-0.65).

4. Discussion

Many papers have examined the prognostic utility of EEG in post-stroke outcome (56 papers for a total of 2,947 participants). There has been a steep increase in the number of papers examining the prognostic utility of EEG in the last decade. This increase may be in part due to improvement in the computing resources to analyze EEG efficiently and in novel ways (e.g., connectivity, dipole/source analysis), along with the emergence of high-density EEG systems.

The majority of papers (52/56, 93%) showed all or some positive prognostic potential of EEG for post-stroke outcomes. Main observations are detailed as follows. First, prognostic potential was evident at all times post-stroke. While the majority of research has focused on prognosis within a few months post-stroke, there is evidence for chronic stroke patients with mean time post-stroke ranging from 11 months[40] to 8 years[44] that EEG is associated with improvement after a subsequent rehabilitation treatment. This evidence is aligned with general evidence of neuroplasticity in chronic stroke.[94,95] This finding is encouraging for the clinical use of EEG for prognosis and also has implications for participant selection in stroke recovery research studies which includes chronic stroke survivors exclusively in many cases. Stroke recovery research studies often result in findings that a treatment works best for a subset of the

study sample. It is possible that EEG would be a useful tool to provide information to explain subsets of non-responders or even to be used as inclusion criteria.

Second, direct comparisons were not made between ischemic and hemorrhagic stroke types. While initial improvement is greater for hemorrhagic stroke compared to ischemic stroke, the time course of recovery does not differ between the two stroke types from 3 months post-stroke.[96] Despite the difference in etiology and initial severity level, response of the brain to the insult as captured by EEG may be relevant for recovery for both stroke types, although this needs to be empirically tested.

Third, among outcome domains, independence was most studied with most positive findings and no negative findings (n=14 only positive, 6 mixed, 0 negative findings). Meta-analysis including 7 papers also supports the strong relationship between EEG and MRS. All papers that examined independence as an outcome were in acute/subacute stroke, with EEG performed on average 6 days post stroke (ranging from a few hours to a month), and outcome measured on average 4 months post stroke (ranging from a week to a year). Therefore, the translational potential of this evidence to standard acute/subacute stroke care is high, as the majority of the evidence is directly from that setting, involving EEG recording while patients rested.

While some ability of EEG to predict outcomes was seen for all outcomes studied, the results from other outcomes, such as upper extremity movement, speech, balance/gait, and cognition, were mixed. For all outcomes, besides sensorimotor, there was more evidence to support the predictive ability of EEG than evidence to refute it. In general, more research with methodological rigor is needed to determine the predictive ability of EEG for these outcomes.

Third, in over 95% of studies, EEG was able to increase prognostic ability compared to using the conventional predictor of initial clinical score alone. This is a critical point in the potential translation of EEG to routine clinical practice. The addition of EEG, while non-invasive, can be cumbersome and adds to cost of care. Evidence that prognostic ability is improved from what can be attained from standard of care is a critical factor in advocating for the addition of routine EEG in post-stroke patients. The practical extent of the consequences of better prognostic ability will need to be explored. It will be important for clinicians and hospital/clinical managers to ultimately realize a quality and/or cost benefit to the addition of prognostic EEG.

Lastly, prognostic potential was likely obscured due to methodological constraints. Variables such as EEG to outcome time, sample size, and number of EEG electrodes used may all contribute to differences in study results. The variety of EEG measures and lack of standardization also may mask results and hinders comparability of study outcomes. In addition, many studies had fair or poor quality evaluations due in large part to data not being fully reported; some quality issues were methodological in nature and may have influenced study results.

Evidence regarding prognostic utility of EEG is largely explorative. The majority of papers were exploratory in nature and did not have a priori hypothesized EEG variable(s) for prognosis. This explorative nature explains the large number of papers with mixed results due to the variety of EEG measures used. This may also explain the moderate relationships between EEG and outcomes such as the NIHSS or FMUE. In general, there is emerging evidence that EEG has the potential to inform clinical decision-making and guide individualized treatment. However, consensus on the best EEG biomarker is needed for clinical translation to occur.

Limitations

Due to publication bias, the prognostic value found in this review may be elevated. However, such bias may have been mitigated since EEG prognosis is typically investigated as a secondary analysis in many papers. In addition, we were conservative in categorizing the results of each paper. Some papers concluded a positive prognostic result, while they were regarded as negative in this review based on the criteria described in the method section. Some papers hypothesized prognosis for one EEG variable and reported negative results for other EEG variable(s) as a negative control, which added to the number of negative findings in this review. Some papers had an objective different from prognosis and happened to report correlations applicable to prognosis. Those results added to the negative results in this review, although these papers may not have chosen an EEG variable best for prognosis. The conservative approach used in this review was to identify a robust biomarker of outcome.

The number of papers included in the meta-analysis was reduced, because some papers applied outcome measures differently (e.g., dichotomization). This review did not include papers that were published in languages other than English.

5. Conclusion

Many studies examined the prognostic utility of EEG in post-stroke outcome in the recent decade. Prognostic evidence was seen at all times post-stroke, with mean time post-stroke ranging from immediately after the stroke[61] to 8 years.[44] The most studied prognostic potential of EEG is in predicting independence in the standard acute/subacute stroke care setting. This finding is also supported by the strong relationship between EEG and MRS found in the meta-analysis. Furthermore, there is evidence that EEG improves prognostic ability beyond the conventional

predictor of the initial clinical score. However, evidence regarding the prognostic utility of EEG is largely explorative, with many EEG measures used, primarily due to the lack of a definitive set of best EEG variables to use for prognosis. With continued advancement in computing capacity that enables source imaging and analysis efficiency, exploration of EEG biomarkers is expected to continue. In summary, EEG shows potential to improve post-stroke prognostic ability and inform clinical management, with a need to identify the best EEG measures for prognosis.

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Declaration of Interest Statement

The authors report no conflicts of interest.

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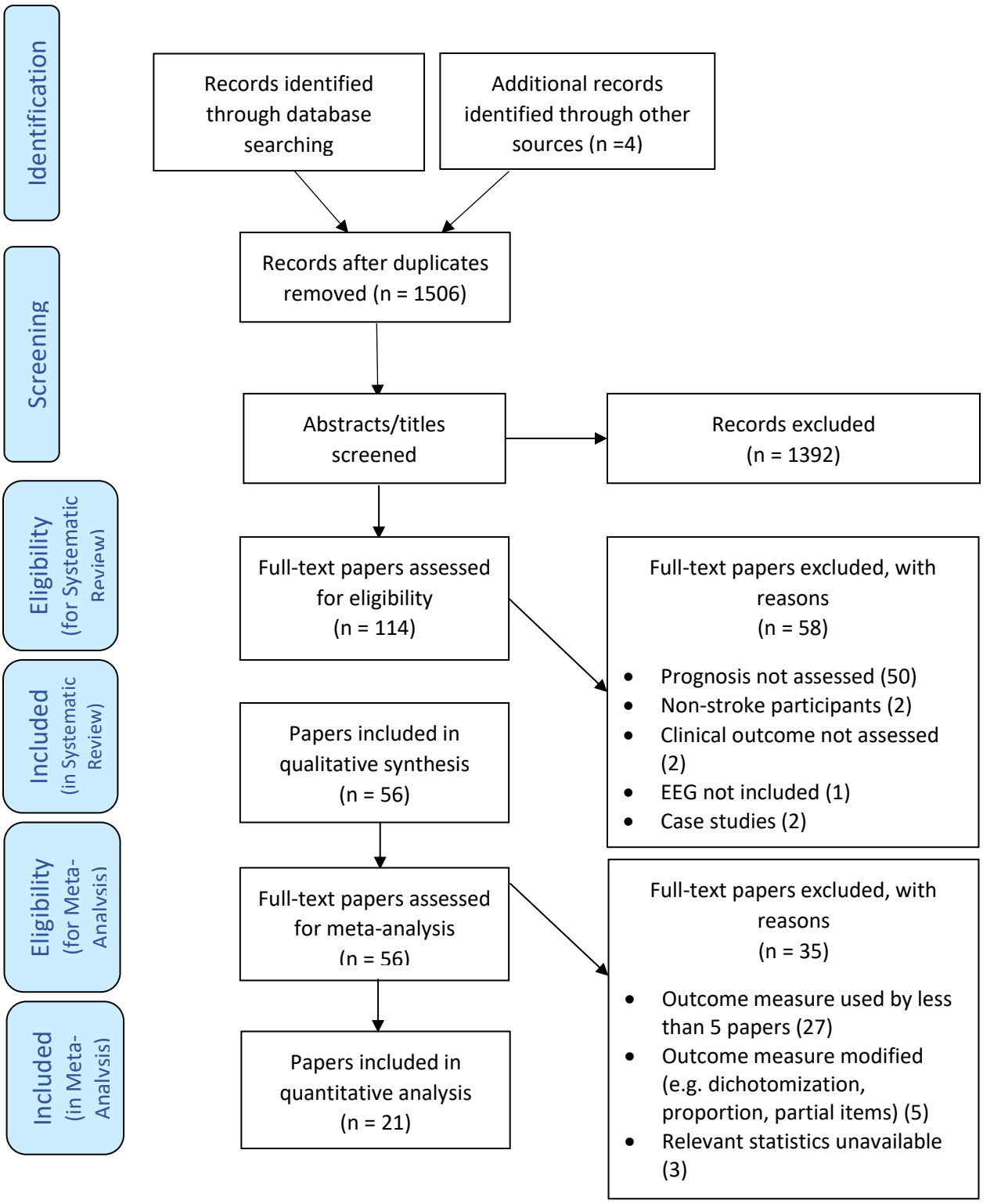


Figure 1. PRISMA 2009 flow diagram.

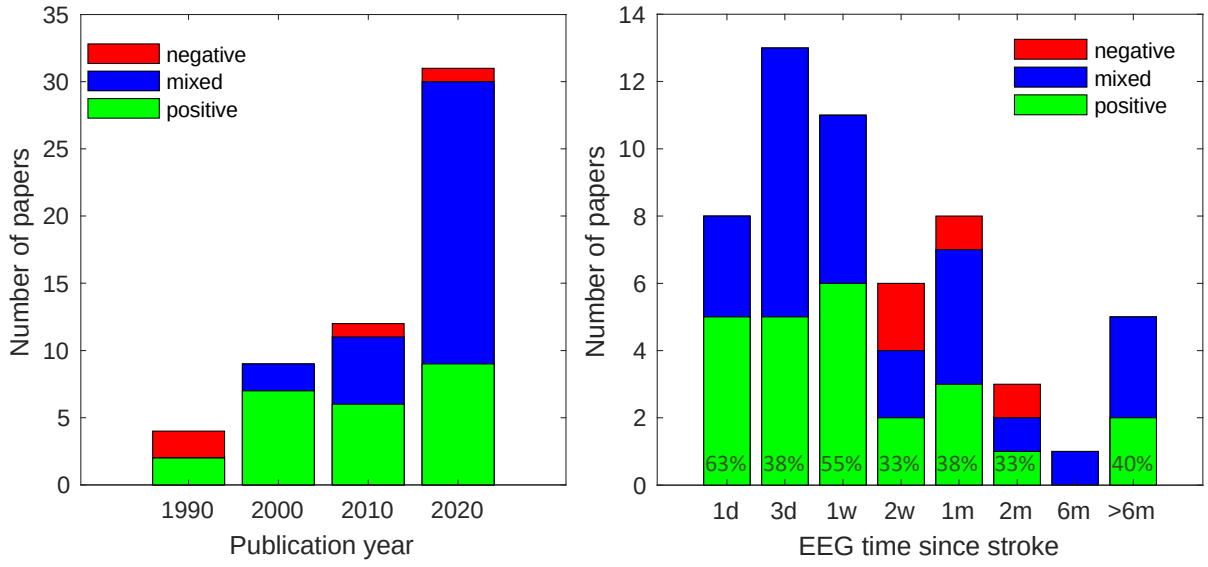


Figure 2. The number of papers published examining prognostic utility of EEG for post-stroke outcome over the years (A) and mean EEG times (B). The histograms shows the number of papers for each time period that reported (i) only positive, (ii) only negative, and (iii) mixed (i.e., both positive and negative) findings for EEG-based prognosis of post-stroke outcome. The upper limit of the bin is noted on the horizontal axis (e.g., bins=1981-1990, … , 2011-2020 in A, 0-1 day, >1 to 3 days, … in B). The last bar in B includes papers with EEG time ranging from 1 to 8 years post stroke. One paper with mixed findings did not report the exact EEG time,[45] thus is not included in B.

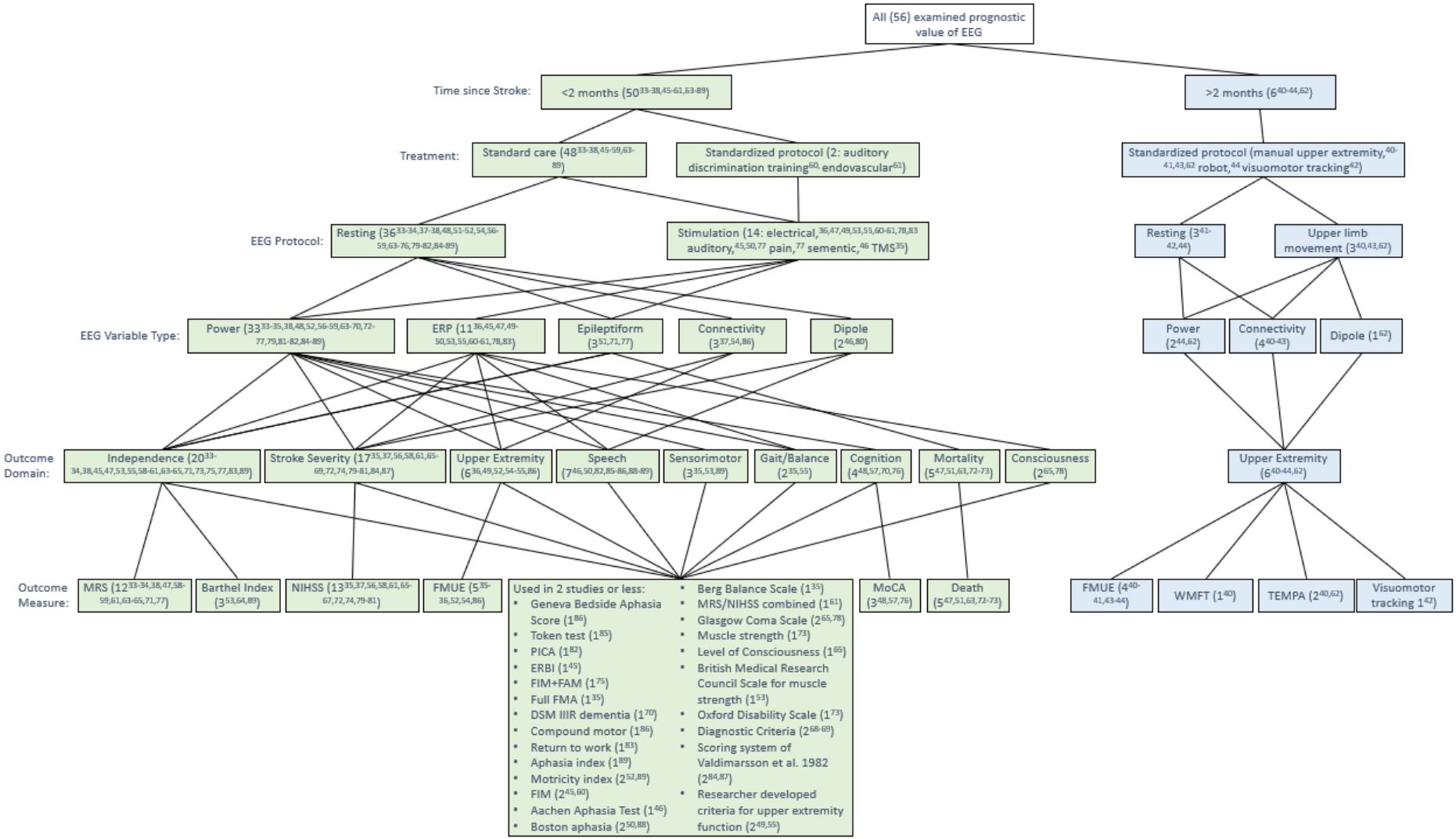


Figure 3. Distribution of papers per study characteristics, including time since stroke, EEG protocol, EEG variable type, outcome domain, and outcome measure shows a lack of uniformity.

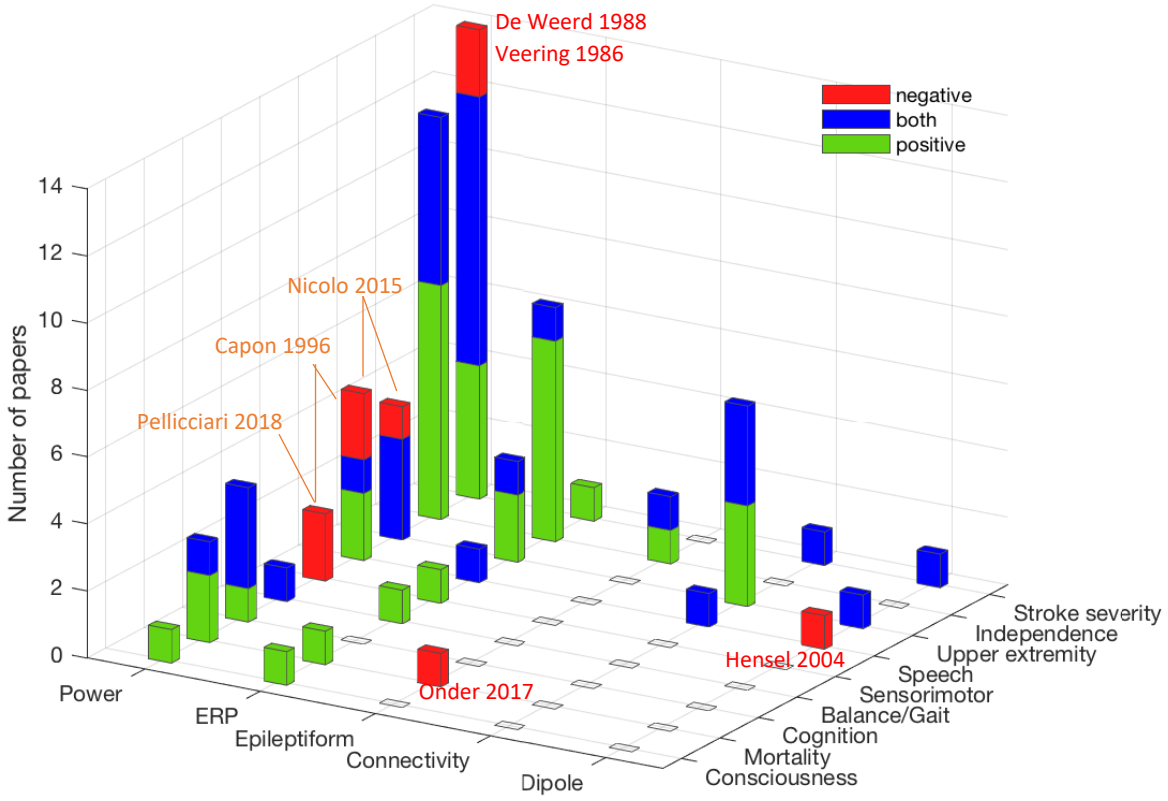


Figure 4. Distribution of outcome domains and EEG variable types examined. Papers that reported (i) only positive, (ii) only negative, and (iii) mixed findings for EEG-based prognosis of post-stroke outcomes are presented in stacked bars. Papers that examined multiple outcome domains and/or EEG variable types are presented for each result. In addition to the 4 papers that showed negative findings in the previous figure,[46,51,84,87] 3 papers reported negative findings in only some of the multiple outcome domains[35,89] or some of the multiple EEG variable types examined.[86]

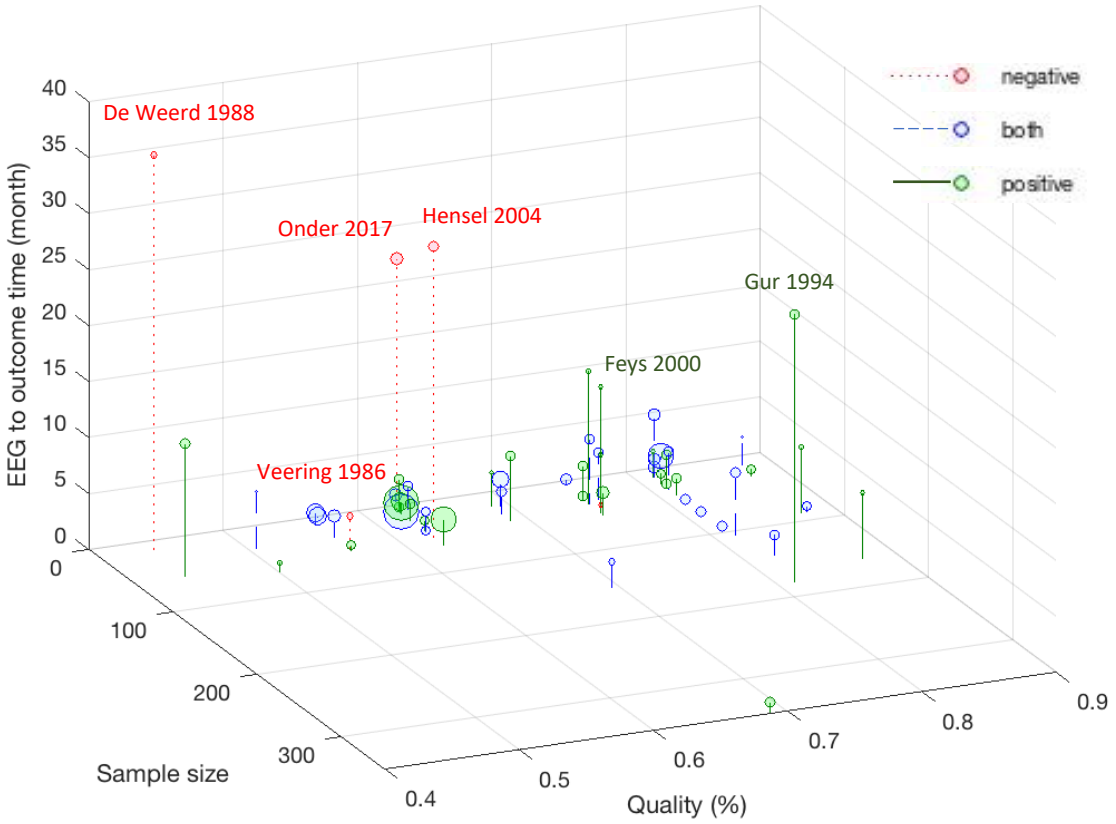
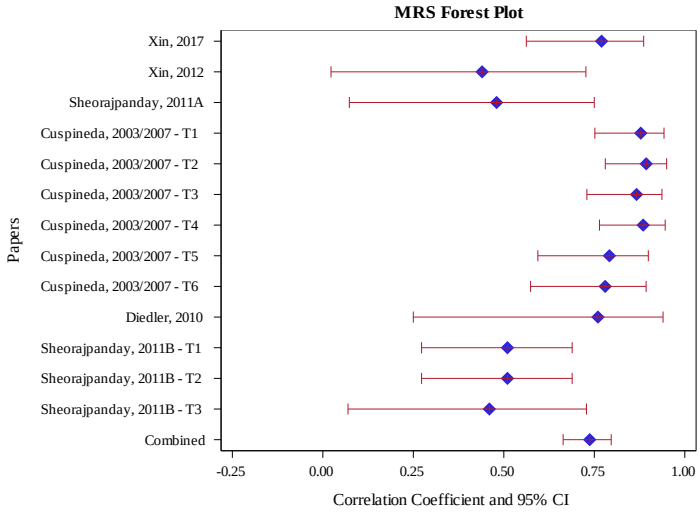
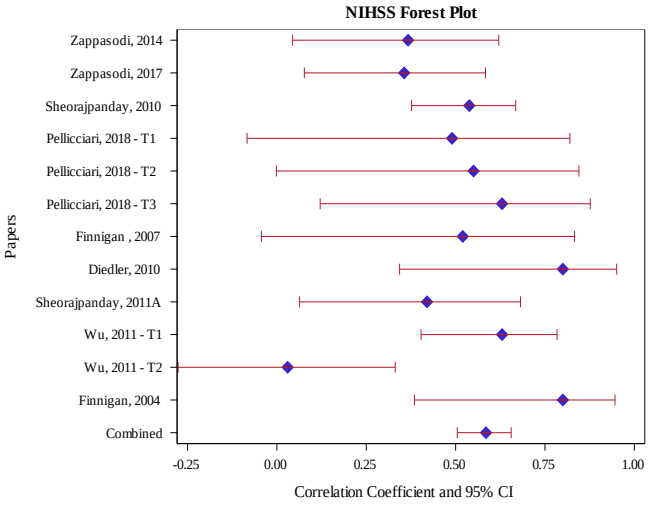


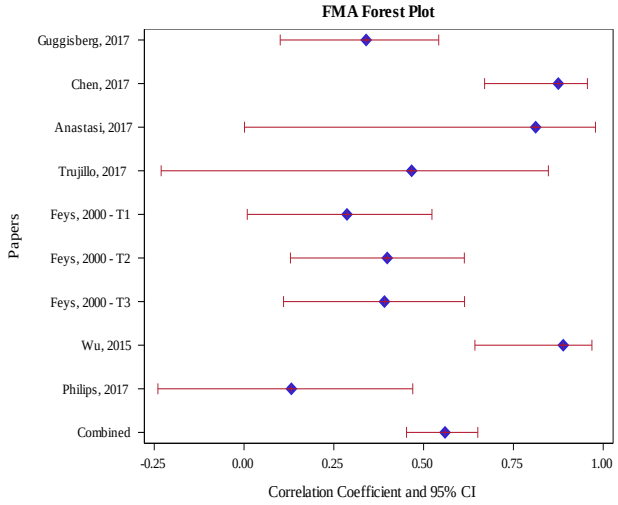
Figure 5. Distribution of the quality score, sample size, EEG to outcome time, and number of EEG electrodes used (denoted by the marker diameter) across papers. Papers that reported (i) only positive, (ii) only negative, and (iii) mixed findings for EEG-based prognosis of post-stroke outcome are presented with the solid, segmented, and dotted lines, respectively. Papers that examined multiple outcome time points are presented for all time points (e.g., one study[36] reported negative findings for 2 months but positive findings for 6 and 12 month outcomes). Papers that did not report information on EEG or outcome times are not included in this figure.



(A)



(B)



(C)

Figure 6. Forest plots showing correlation coefficients between EEG and outcome with 95% confidence interval for MRS (A), NIHSS (B), and FMUE (C).

Chapter 3: Aim 2

Manuscript 2:

Using Subthreshold Vibratory Stimulation During Post-Stroke Rehabilitation Therapy:

A Case Series

Using subthreshold vibratory stimulation during post-stroke rehabilitation therapy: a case series

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Declaration of Interest Statement

N.J. Seo is an inventor of a patent regarding the investigated sensory stimulation. The other authors report no conflicts of interest.

Ethics Approval

The study protocol was approved by the Institutional Review Board at the Medical University of South Carolina (Pro00074041).

Clinical Trial Registration

Clinical trial Identifier: NCT03473808

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Abstract

Background: Subthreshold vibratory stimulation to the paretic wrist has been shown to prime the sensorimotor cortex and improve 2-week upper extremity (UE) therapy outcomes.

Objective: To determine feasibility, safety, and preliminary efficacy of the stimulation over a typical 6-week therapy duration.

Methodology: Four chronic stroke survivors received stimulation during 6-week therapy. Feasibility/safety/efficacy were assessed at baseline, post-therapy, and 1-month follow-up.

Results: For feasibility, all participants wore the device throughout therapy and perceived the stimulation comfortable/safe. Regarding safety, no serious/moderate intervention-related adverse events occurred. For efficacy, all participants improved in Wolf Motor Function Test and UE use in daily living based on accelerometry and Stroke Impact Scale. Mean improvements at post-therapy/follow-up were greater than the minimal detectable change/clinically important difference and other trials with similar therapy without stimulation.

Conclusion: The stimulation was feasible/safe for 6-week use. Preliminary efficacy encourages a larger trial to further evaluate the stimulation as a therapy adjunct.

Keywords: Stroke rehabilitation, upper extremity, paresis, subliminal stimulation, physical stimulation, patient safety

Introduction

Stroke is a leading cause of long-term disability in the United States (Virani et al., 2020). Upper extremity (UE) impairment affects 65% of stroke survivors at 6 months post-stroke (Dobkin & Carmichael, 2016). UE impairment limits stroke survivors' ability to perform functional tasks, thus reducing independence (Stewart & Cramer, 2013). Given limited time and resources allotted for therapy (Lynch et al., 2017). post-stroke treatment must be optimized to maximize recovery.

One approach to enhance motor recovery is the use of sensory stimulation as a therapy adjunct (Conforto et al., 2018). Sensory stimulation facilitates changes in the primary motor cortex (Baker, 2007; Schabrun et al., 2012) and associated motor output (M. Ridding & J. Rothwell, 1999) via direct neuronal projections from the sensory to motor areas (Chen & Ashby, 1993; Jenner & Stephens, 1982). As such, meta-analysis showed that application of sensory stimulation immediately prior to therapy enhanced UE motor recovery more than therapy without stimulation (Conforto et al., 2018). However, the existing sensory stimulation method requires patients to remain in a sedentary position for 2 hours while receiving stimulation (Bastos Conforto et al., 2010; Carrico, Chelette, II, et al., 2016; Carrico, Chelette, Westgate, et al., 2016; Celnik et al., 2007; Conforto et al., 2007) and the effect diminishes once the stimulation is removed (Kaelin-Lang et al., 2002; Smith & Brouwer, 2005).

To address these limitations, a novel sensory stimulation was recently developed. Specifically, the new stimulation uses a wearable wristband to apply subthreshold random-frequency vibratory stimulation to the paretic wrist *during* therapy. Thus, the effect of the stimulation may remain potent during therapy tasks because it is delivered continuously during therapy. In addition, the new stimulation does not interfere with therapy tasks because the device is compact and wearable and the stimulation is imperceptible. Using this stimulation eliminates

the need for patients to receive stimulation in a sedentary position prior to therapy. Therefore, the new stimulation may offer advantages that might promote translation to clinical practice.

Preliminary studies have shown that the new stimulation primes the sensorimotor cortex for the hand (Seo et al., 2015; N. J. Seo, K. Lakshminarayanan, et al., 2019). Specifically, sensory processing activity in the sensory cortex measured by electroencephalography increased when the stimulation was applied (Seo et al., 2015), explaining enhanced sensation with the stimulation in chronic stroke survivors (Enders et al., 2013). Since sensory input affects motor output (M. C. Ridding & J. C. Rothwell, 1999), the new stimulation has also been shown to increase brain activity for hand grip tasks (N. J. Seo, K. Lakshminarayanan, et al., 2019), explaining improved hand grip performance with the new stimulation in chronic stroke survivors (Seo et al., 2014). Thus, the new stimulation may have a potential to facilitate neural plasticity and recovery of hand function post-stroke. A 2-week pilot randomized controlled study showed that use of this stimulation during task-practice therapy increased UE motor function more than therapy without stimulation (N. J. Seo, M. L. Woodbury, et al., 2019).

However, use of this stimulation over a longer treatment duration typical in standard rehabilitation, such as 6 weeks, has not been examined. Clinicians and peer scientists have expressed serious concerns that longer exposure to the stimulation may cause patients to become desensitized to UE sensory input and/or dependent on the stimulation, resulting in worse sensory and/or motor function. Thus, it is critical to examine whether patients exhibit deterioration of sensation with safety concerns and a lack of motor improvement after 2 weeks of treatment, possibly resulting in patients' refusal of the stimulation. Therefore, the purpose of this study was to determine feasibility, safety and preliminary efficacy of using this stimulation during a typical 6-week therapy duration.

Materials and Methods

Participants

The study protocol was approved by the Institutional Review Board. All participants provided written informed consent. Participants were included if they were adults at least 6-months post-stroke with moderate UE impairment (Fugl-Meyer Assessment Upper Extremity score 19-47) (Woodbury et al., 2013) with the ability to participate in UE therapy. Participants were excluded if they had (1) complete UE deafferentation, (2) UE rigidity, (3) botulinum toxin injection in the paretic UE within 3 months (Setler, 2002) prior to/during enrollment, (4) brainstem stroke, (5) comorbidity, such as orthopedic conditions, peripheral neuropathy of the hand, or compromised skin integrity of the wrist, (6) concurrent UE therapy, or (7) language barrier/cognitive impairment that precluded following 3-step instructions and/or providing consent.

Experimental Design

A single-arm pilot study was conducted. All participants received in-lab task-practice therapy with an occupational therapist while wearing a stimulation device on the paretic wrist (figure 1). Therapy was approximately 2 hours/session, 3 sessions/week for 6 weeks, for a total of 18 sessions, resembling a typical outpatient therapy schedule.

[Figure 1 near here]

Therapy followed a standardized manual with activities to address manual dexterity. The manual (N. J. Seo, M. L. Woodbury, et al., 2019) was developed by experienced therapists based

on the EXCITE trial (Wolf et al., 2006) manual and Task Specific Practice (Lang & Birkenmeier, 2014). Each session, participants practiced 2 in-hand manipulation tasks and 2 tasks involving reaching to grasp/place objects. The therapist and participant collaboratively selected tasks relevant to the participant's daily living. To standardize therapy dosage, participants completed 300 UE movement repetitions per session (75 per task). The manual defined a repetition for each task to ensure consistency in counting repetitions. Tasks were adjusted to achieve a difficulty level that was "just-right" for each participant. The right difficulty level was achieved by changing the weight, size, shape, and location of the object, using adaptive materials (e.g., nonslip mat to prevent items from moving) as needed, and adjusting task complexity, instruction, movement speed, and accuracy. Participants were also encouraged to practice the tasks in-home and use the paretic UE in daily activities.

The stimulation device (figure 1) was composed of a vibrator (C-3 Tactor, EAI, Casselberry, FL) and MP3-playing watch (Amazon). The device delivered random-frequency vibration (with white noise signal low-pass filtered at 500 Hz) to the wrist at 60% of the sensory threshold (i.e., imperceptible to the participant), continuously throughout each therapy session. These vibration parameters were selected because they yielded consistent, reproducible, statistically significant improvement in hand function in previous studies (Enders et al., 2013; Lakshminarayanan et al., 2015; Seo et al., 2014; Seo et al., 2015; N. J. Seo, M. L. Woodbury, et al., 2019). The participants' sensory threshold was determined at the beginning of each therapy session by increasing or decreasing the vibration intensity until the participant verbally indicated they could or could not perceive the vibration, respectively (Ehrenstein & Ehrenstein, 1999; N. J. Seo, M. L. Woodbury, et al., 2019). The stimulation device was not worn outside therapy.

Feasibility

First, the therapist observed whether the participants wore the device and monitored participants' reactions throughout therapy sessions. Second, participants' perceived comfort and safety in receiving the stimulation from the device during therapy were obtained on a 7-point Likert scale (1=strongly agree, 7=strongly disagree) post-intervention. In addition, to determine if the vibration was indeed imperceptible, the therapist asked participants if they felt vibration after each therapy session.

Safety

Adverse events (AEs) were identified according to the criteria/schedule in table 1. AEs were evaluated for severity (US Department of Health and Human Services, 2017) and relatedness to the intervention (NINDS, 2017). The severity and relatedness categorizations were approved by the Data and Safety Monitoring Board.

[Table 1 near here]

Preliminary Efficacy

The effect of the intervention on motor function was assessed using the Wolf Motor Function Test (WMFT) (Wolf et al., 2001) time and Box and Block Test (BBT) (Chen et al., 2009). Translation of improved motor function to paretic UE use in daily living was assessed using the objective accelerometer measure (Waddell et al., 2017), patient-perceived measure of the Stroke Impact Scale (SIS) hand and activities of daily living (ADL) subscales, and self-reported benefits. For accelerometers, participants wore an ActiGraph GT9X Link (ActiGraph,

Pensacola, FL) on the paretic wrist outside therapy for 3 days. The total number of hours per day that the paretic UE was active was computed. All assessments were administered at baseline, post (within 1-week after the last therapy session), and 1-month follow-up. Additionally, WMFT and accelerometer were assessed after each week of therapy to examine the trend of change over time.

To ensure reliability, WMFT and BBT were videotaped and scored by blinded raters trained on standard scoring procedures (Mathiowetz et al., 1985; Taub et al., 2011). Videos were coded so raters did not know the time of the assessment (before, when during treatment, or when after treatment). Inter-rater and intra-rater reliabilities were assessed using Spearman correlation using scores from all assessment times and subjects. Interrater reliability was 0.999 for WMFT and 1.0 for BBT. Intra-rater reliability was 1.0 for both WMFT and BBT.

Changes in UE motor function and use in daily living were examined for individual participants and compared to the minimum detectable change (MDC) and minimal clinically important difference (MCID) to gauge whether they were beyond measurement error and clinically relevant, respectively. In addition, week-to-week changes in WMFT and accelerometer data were visually examined for any trend over time. Furthermore, the changes were compared to other published trials with similar manual therapy but without stimulation. This historical comparison was to gauge if the addition of stimulation to therapy might improve UE outcomes more than therapy without stimulation. Specifically, WMFT, SIS, and accelerometer data were historically compared because those measures were reported in previous trials with similar manual therapy.

Results

Participants

Four participants completed the study. Participants had the mean age of 69 (SD=6) years, mean time post-stroke of 6 (SD=7, range=1.6-16) years, and mean baseline FMUE score of 33 (SD=12, range=22-46).

Feasibility

All participants completed 18 therapy sessions while wearing the stimulation device, with no requests to remove it at any time, as observed by the therapist. Participants perceived that the stimulation was comfortable (median=2, range=1-2 on the 7-point Likert scale) and safe (median=2.5, range=1-4) during therapy. The vibration remained imperceptible, as all participants reported that they did not feel vibration during any therapy session.

Safety

No serious AEs were observed throughout the study. No moderate AEs related to the intervention were observed. Only one participant experienced mild AEs with reasonable possibility of being related to the intervention, which were skin irritation on the paretic elbow during one therapy session and increased Monofilament scores on the 5^{th} digit pad at post and follow-up (3.61) compared to baseline (2.44). All AEs are detailed in supplement 1.

Preliminary Efficacy

Changes in UE Motor Function

All participants improved in WMFT time at post and follow-up compared to baseline (figure 2A). Mean improvement in WMFT time was 10 sec (SD=7) at post and 14 sec (SD=11)

at follow-up. These improvements in WMFT time were beyond MDC (0.7 (Fritz et al., 2009) or 4.36 (Lin et al., 2009) secs). However, mean improvement in BBT did not exceed MDC (5.5 blocks) (Chen et al., 2009) (figure 2B).

[Figure 2 near here]

Changes in UE Use in Daily Living

All participants moved their paretic UE more in daily living at post and follow-up compared to baseline, as seen by increased hours of UE use from accelerometers (figure 2C). All participants also improved on SIS-hand (figure 2D) and 3 of 4 improved on SIS-ADL (figure 2E) at post and follow-up compared to baseline. The mean increase for SIS-hand was 21 and 18 at post and follow-up, which was above MCID (17.8 (Lin et al., 2010)). For SIS-ADL, the mean increase was 15 and 18 at post and follow-up, which was above MCID at post and follow-up and MDC at follow-up (5.9 (Lin et al., 2010) and 17.3 (Lin et al., 2010), respectively). Furthermore, all participants had self-reported benefits in using the paretic UE in daily living, as summarized in supplement 2.

Week-to-Week Changes

A trend of continuous improvement over the study period was observed for UE motor function measured by WMFT time (figure 3A). A similar trend was observed also for UE use in daily living as measured by the active hours for the paretic UE using the accelerometer (figure 3B).

[Figure 3 near here]

Comparison to Other Trials

Mean UE improvements were greater in our study than those in other trials using similar manual therapy without stimulation. Specifically, mean improvement in WMFT time was greater in our study than in other large trials (Lo et al., 2010; Winstein et al., 2016) (figure 4A). In addition, mean increase in hours of paretic UE use from accelerometers was higher in our study than in another trial (Waddell et al., 2017) at post (24% vs. 4% increase, or 35 vs. 10 min more per day from baseline, only post data available in the other trial (Waddell et al., 2017)). Similarly, mean increases in SIS-hand and SIS-ADL were higher in our study than in other trials (Birkenmeier et al., 2010; Lang et al., 2016) (figure 4B-C, only post data available for one trial (Lang et al., 2016)).

[Figure 4 near here]

Discussion

This study investigated feasibility, safety, and preliminary efficacy of using subthreshold random-frequency vibratory stimulation during 6-week task-practice therapy. This study extends the previous 2-week study (N. J. Seo, M. L. Woodbury, et al., 2019) in the following ways.

Feasibility/Safety Over a Longer Therapy Duration of 6 Weeks

First, we found that the stimulation was feasible and safe to use over a longer therapy duration of 6 weeks. For safety, the mild skin irritation experienced by one participant likely

resulted from the elbow rubbing on an armrest, which could occur during any therapy intervention or in daily living. Increased Monofilament scores may have been influenced by the little to moderate reliability of the test (Bulut et al., 2018), since other sensory measures did not decline for this participant. Specifically, s/he did not develop perceived numbness and had improved two-point discrimination scores from fair (6-8 mm) to normal (5 mm) for all digits at this time. In addition, this person frequently experienced skin irritation prior to the study, which may be related to the change in the Monofilament score. This finding extends previous reports of safety in using this stimulation over 2 (N. J. Seo, M. L. Woodbury, et al., 2019) and 4 (Na Jin Seo et al., 2019) weeks.

Continuous, Detectable, and Sustained Improvement in UE Motor Function

Second, this study extends the previous study by showing that continued use of the stimulation during therapy beyond 2 weeks may yield additional UE improvements, as seen by the trend of continuous UE improvement over 6 weeks. This trend of continuous UE improvement without deterioration supports use of the stimulation over a longer rehabilitation duration.

Specifically, every participant improved UE motor function as assessed by WMFT time at post and follow-up compared to baseline. Mean improvement in WMFT time was greater than MDC for post and follow-up, indicating that the improvement was beyond measurement error. Further, mean improvement at post was retained at 1-month follow-up. This finding indicates that the 6-week treatment resulted in detectable and sustained improvement in UE motor function.

While participants in the present study had improvements in WMFT time, they did not improve on BBT. This finding contrasts the trend found in the previous 2-week study in which improvement was more prominent in BBT than WMFT time (N. J. Seo, M. L. Woodbury, et al., 2019). These different findings may be explained by different participant characteristics. Specifically, participants in the present study had greater impairment at baseline compared to those in the previous study (WMFT hand-task time mean±SD = 76±48 vs. 14±15 sec, BBT = 9±11 vs. 29±14 for the present study and previous study (N. J. Seo, M. L. Woodbury, et al., 2019), respectively). It is possible that while our participants were able to improve WMFT time, the improvement was not sufficient to change BBT scores. For example, two participants had WMFT hand-task time of 114 and 115 sec at baseline. While they were able to substantially improve the time to 75 and 86 sec at follow-up, such time is still longer than the 60 sec time limit imposed for BBT. Consequently, their BBT scores remained at 1 from baseline to follow-up.

Clinically Meaningful/Sustained Impact on UE Use in Daily Living

Third, this study extends the previous study by showing that the improved UE motor function seen in WMFT time translated from the laboratory to UE use in daily living in meaningful ways. Specifically, all participants had less difficulty using their paretic hand to perform daily tasks at post and follow-up compared to baseline, based on SIS. Mean difficulty level lessened from “very difficult” to “somewhat difficult” for SIS-hand items, such as turning a doorknob and opening a can. Mean difficulty level lessened from “somewhat difficult” to “a little difficult” for SIS-ADL items, such as dressing and bathing oneself. Mean improvements in SIS were greater than MCID, indicating that the intervention led to clinically meaningful changes in the participants’ perceived abilities in daily living.

Clinical meaningfulness is further highlighted by participants' self-reported benefits. All participants reported benefits, in a variety of domains including ADLs (e.g., self-feeding, self-care), instrumental ADL (e.g., meal preparation), leisure, and vocation. As a result, participants experienced increased ability to integrate into society and participate within the community, such as dining at restaurants and mini-golfing with family. These perceived improvements in UE use in daily living from SIS and self-reports were consistent with the objective measure using accelerometers, showing that every participant increased the duration of paretic UE use in daily living.

Historical Comparisons

Since this case series study did not include a control group, we performed historical comparison to other trials in the literature. Historical comparisons show that mean UE improvements observed in our study were greater than those in other trials with similar manual therapy without stimulation. This comparison suggests that addition of the stimulation might improve UE motor function and use in daily living more than therapy without stimulation.

In the historical comparisons, greater mean improvements were obtained despite no difference and/or inferiority in baseline function, time post-stroke, and intervention length. Specifically, for baseline, our mean WMFT time of 50 (SD=37) sec was within the ranges of the other trials (mean±SD = 74±30 sec (Lo et al., 2010) and 17±19 sec (Winstein et al., 2016)). For UE use in daily living, mean baseline levels were lower in our participants than other trials (51% fewer hours of paretic UE use per day (Waddell et al., 2017); SIS-hand mean±SE = 31±14 for our study vs. 43±6 (Birkenmeier et al., 2010), 47±3 (Lang et al., 2016); SIS-ADL mean±SE = 61±7 for our study vs. 69±4 (Birkenmeier et al., 2010), 63±2 (Lang et al., 2016)). Secondly, our

participants were more chronic on average than the other trials (time post-stroke mean±SD (range) = 6.2±6.6 (1.6-16) years for our study vs. 0.1±0.1 years (Winstein et al., 2016), 4.8±4.0 years (Lo et al., 2010), 1 (0.5-18.4) years (Lang et al., 2016; Waddell et al., 2017), and 3.2 (0.5-10) years (Birkenmeier et al., 2010)). Third, our intervention duration was shorter than or equal to the other trials (6 weeks for our study vs. 10 weeks (Winstein et al., 2016), 12 weeks (Lo et al., 2010), 6 weeks (Birkenmeier et al., 2010), and 8 weeks (Lang et al., 2016; Waddell et al., 2017)).

Limitations and Future Direction

Primary limitations are the small sample and lack of control group. While the previous study using the stimulation (N. J. Seo, M. L. Woodbury, et al., 2019) was a randomized controlled study, the sample was still small. Therefore, a larger randomized controlled trial is needed to confirm the efficacy of the stimulation during therapy compared to therapy without stimulation. For intervention duration, since this study shows a trend of continuous improvement over the 6-week intervention period, future studies may investigate at least 6 weeks of intervention to achieve maximal effects while further examining duration effects of the stimulation.

Conclusion

In summary, this study demonstrates that use of the stimulation during 6-week therapy was feasible and safe, and resulted in continuous, detectable, clinically meaningful, and sustained UE improvements, with translation to daily living, that could be greater than therapy alone as seen in historical comparisons. The present study, together with the previous pilot randomized

controlled study (N. J. Seo, M. L. Woodbury, et al., 2019), collectively suggest a potential that the stimulation may be a promising therapy adjunct to improve post-stroke UE recovery beyond therapy alone.

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Table 1

Adverse event criteria and assessment time. All criteria are compared to the baseline.

Adverse Event Criteria	Time of Assessment
Modified Ashworth scale (spasticity) increase more than 1[47]	Assessed weekly
Pain increase more than 2 on a visual analog scale 0-10	
Emergence of numbness	
Emergence of swelling based on wrist circumference	
UE motor function score decrease more than the Minimum Detectable Change (BBT decrease more than 5.5[35] or WMFT time increase more than 4.36 sec[40])	
Any other self-reported adverse events	
Emergence of skin irritation	
Monofilament or two-point discrimination increase by more than 2 levels and by a category on 1^{st}, 2^{nd}, and 5^{th} digit pads	Assessed at pre, post, follow-up

Figure 1. The stimulation device (circled) was worn on the paretic wrist and delivered subthreshold vibration during task-practice therapy addressing upper extremity motor function, such as the ability to use a screwdriver.

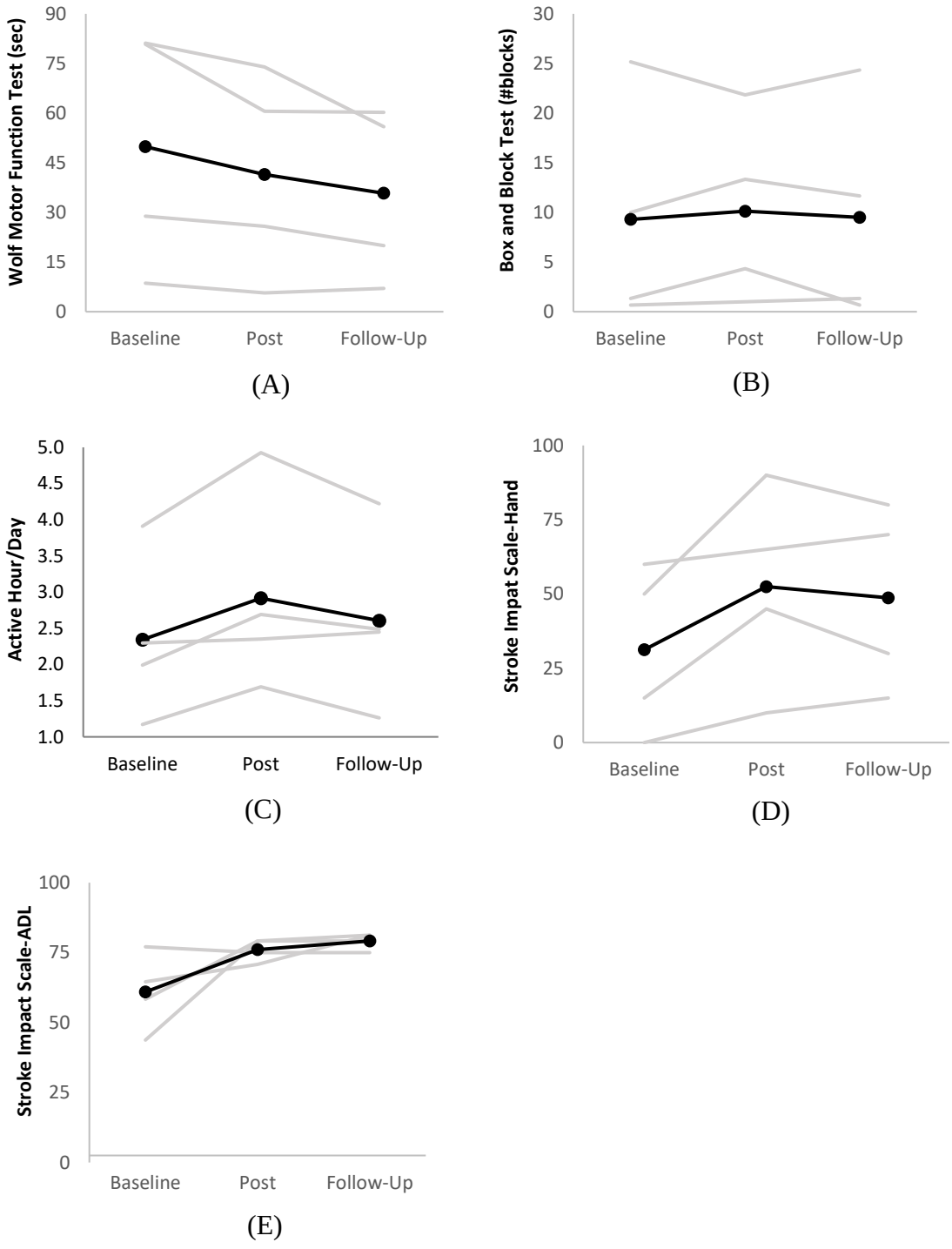


Figure 2. Mean and individual scores on the Wolf Motor Function Test time (A), Box and Block Test (B), hours of paretic upper extremity use per day measured by the accelerometer (C) and Stroke Impact Scale - Hand (D) and Activities of Daily Living (ADL) subscales (E). Darker lines represent the mean and lighter lines represent individual participant scores.

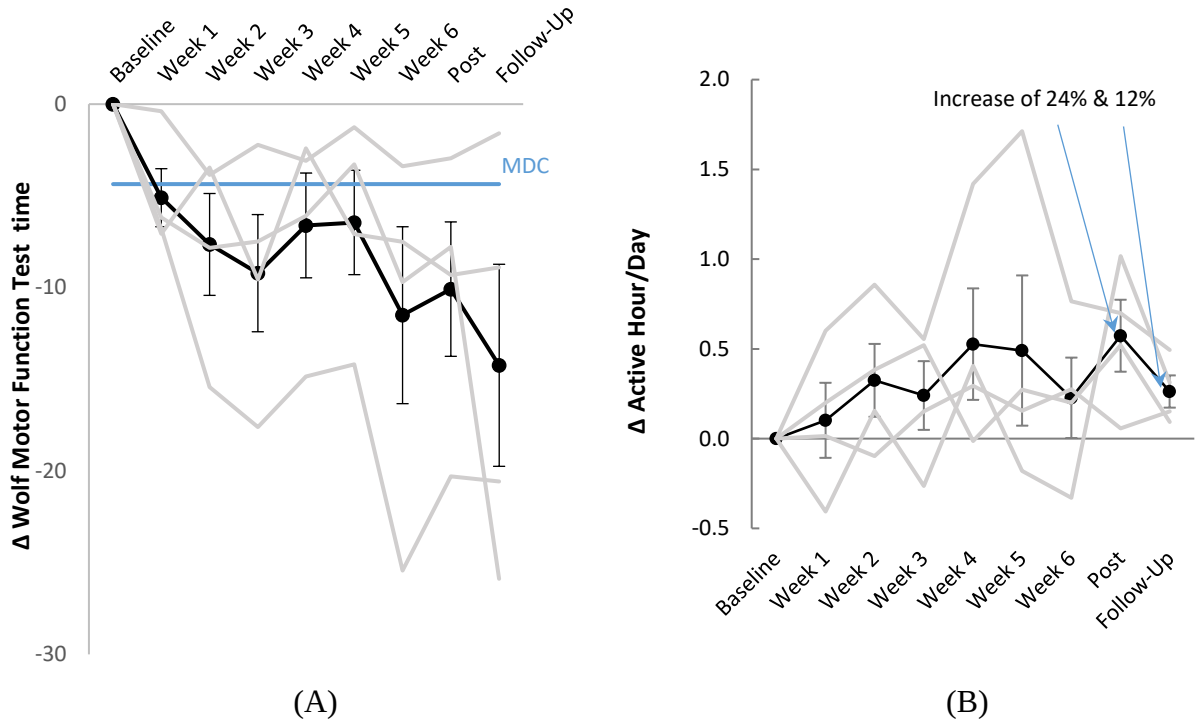
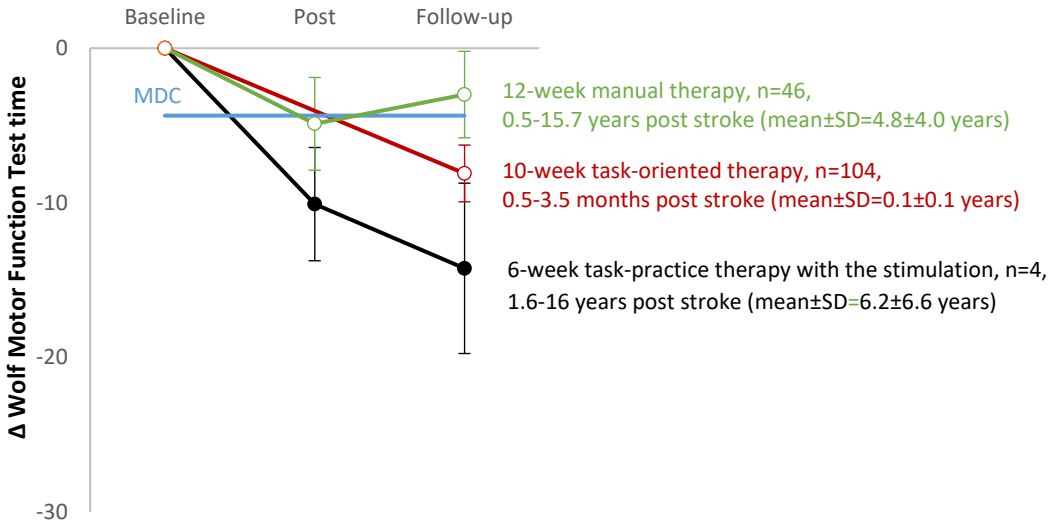
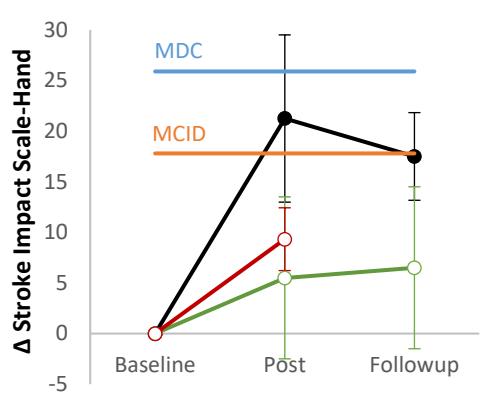


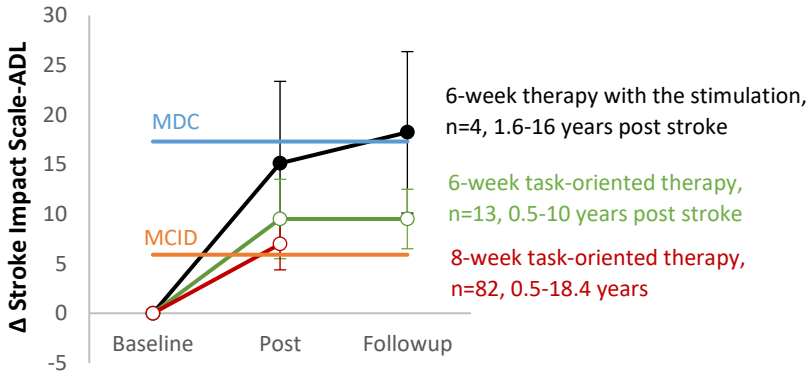
Figure 3. Week-to-week change in the Wolf Motor Function Test (WMFT) time (A) and hours of paretic upper extremity use per day measured by the accelerometer (B). The mean and standard error of the changes are shown. The Minimum Detectable Change (MDC) for WMFT (Lin et al., 2009) is also shown (A).



(A)



(B)



(C)

Figure 4. Comparison to other trials. (A) Change in the Wolf Motor Function Test time compared to other large trials with similar manual therapy of 10 (Winstein et al., 2016) and 12 (Lo et al., 2010) weeks. The mean and standard error (SE) of the change are shown. Minimum detectable change (MDC) (Lin et al., 2009) is also shown. Changes in the Stroke Impact Scale - Hand (B) and Activities of Daily Living (ADL) subscales (C) are compared to other trials with similar manual therapy of 6 (Birkenmeier et al., 2010) and 8 (Lang et al., 2016) weeks. The mean and SE of the change score are shown for the present study. The mean change and SE of the raw score are shown for other trials because SE of the change was not provided. Minimum detectable change (MDC) (Lin et al., 2010) and minimal clinically important difference (MCID) (Lin et al., 2010) are also shown.

Chapter 4: Aim 3

Manuscript 3:

Predicting Upper Extremity Motor Improvement Following Therapy using EEG-based Connectivity in Chronic Stroke

Predicting Upper Extremity Motor Improvement Following Therapy using EEG-based Connectivity in Chronic Stroke

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Abstract

Background: Uncertain prognosis presents a challenge for therapists in determining the most efficient course of rehabilitation treatment for individual patients. Cortical Sensorimotor network connectivity may have prognostic utility for upper extremity motor improvement because the integrity of the communication within the sensorimotor network forms the basis for neuroplasticity and recovery.

Objective: To investigate if pre-intervention sensorimotor connectivity predicts post-stroke upper extremity motor improvement following therapy.

Methods: Secondary analysis of a pilot triple-blind randomized controlled trial. Twelve chronic stroke survivors underwent 2-week task-practice therapy, while receiving vibratory stimulation for the treatment group and no stimulation for the control group. EEG connectivity was obtained pre-intervention. Motor improvement was quantified as change in the Box and Block Test from pre to post-therapy. The association between ipsilesional sensorimotor connectivity and motor improvement was examined using regression, controlling for group. For negative control, contralesional/interhemispheric connectivity and conventional predictors (initial clinical motor score, age, time post-stroke, lesion volume) were examined.

Results: Greater ipsilesional sensorimotor alpha connectivity was associated with greater upper extremity motor improvement following therapy for both groups ($p<0.05$). Other factors were not significant.

Conclusion: EEG connectivity may have a prognostic utility for individual patients' upper extremity motor improvement following therapy in chronic stroke.

Keywords: EEG, stroke, rehabilitation, upper extremity, paresis, subliminal stimulation, physical stimulation, prognosis

1. Introduction

Stroke is a leading cause of long-term disability that affects nearly 800,000 people in the United States each year.[1] Of those affected by stroke, 77% experience upper extremity (UE) impairment that reduces the individuals' ability to perform daily tasks independently.[2] However, the extent of recovery varies widely among stroke survivors.[3] Uncertain prognosis for UE motor recovery presents a hurdle in developing personalized UE rehabilitation treatment plans for individual patients. Improved prognosis may guide therapists to set realistic therapy goals related to UE function and choose the maximally efficient course of treatment for their patients.

Many studies have investigated conventional predictors of UE motor recovery including initial clinical motor score, age, time post-stroke, and lesion volume.[4] Meta-analysis shows that age, time post-stroke, and lesion volume do not predict recovery, while initial clinical motor score is the most significant predictor.[4] However, the effect sizes for initial clinical motor scores have recently been shown to be inflated, meaning the strength of the association between initial clinical motor scores and recovery may be overly optimistic.[5,6]

Sensorimotor network connectivity, measured using electroencephalography (EEG), may have prognostic utility for UE motor recovery, because the integrity of the communication between sensorimotor cortices forms the basis for neuroplasticity and motor recovery.[7] Previous studies have found the prognostic potential of EEG connectivity for post-stroke UE recovery.[8-13] However, previous studies have largely examined prognosis using EEG channel-based connectivity analysis,[9-13] as opposed to patient-specific source analysis.[14] It is important to model EEG sources using patient-specific brain magnetic resonance imaging (MRI) in stroke to take the lesion into account.[14] Furthermore, previous studies have investigated only one type of rehabilitation intervention within each study.[8-13] Therefore, how prognosis changes depending on the type of rehabilitation intervention has yet to be examined.

Therefore, the objective of this study was to investigate prognostic potential of sensorimotor connectivity from patient-specific EEG source modeling for UE motor improvement following two rehabilitation treatment. This study utilized data from a previously published pilot triple-blind randomized controlled trial[15] in which one group of chronic (>6 months post-stroke) stroke survivors received UE task practice therapy and subthreshold vibratory stimulation and the other group of chronic stroke survivors received UE task practice therapy only. It was hypothesized that greater EEG sensorimotor connectivity prior to rehabilitation treatment is associated with greater UE motor improvement for both groups.

2. Methods

2.1 Participants

This study entails a secondary analysis from a triple-blind randomized controlled trial.[15] Participants were included if they were adults (21-80 years) at least 6-months post-stroke with mild-to-moderate UE impairment based on Fugl-Meyer Upper Extremity Assessment scores (30-60/66 points). Participants were excluded if they (1) exhibited cognitive impairment such as the inability to follow 3-step instructions, (2) had botulinum toxin injection in the paretic UE within 3 months of enrollment, or (3) participate in other UE therapy sessions. A total of 12 participants completed the study. Participants had the mean age of 62 (SD=8), mean time post-stroke of 5 (SD=5) years, and baseline FMUE score of 48 (SD=8). Baseline demographic characteristics, including age, time post-stroke, and Fugl-Meyer Upper Extremity scores, were not significantly different between groups.[15] The study protocol was approved by the Medical University of South Carolina's Institutional Review Board. All participants provided written informed consent.

2.2 Study Design

Participants were randomly assigned to the treatment or control group (n=6/group). All participants received in-lab task-practice therapy[16] for 2 hours/session, 3 sessions/week for 2 weeks. All participants also wore a vibrator (C-3 Tactor, EAI, Casselberry, FL) on the paretic wrist during therapy.[15] The treatment group received imperceptible random-frequency vibration at 60% of the sensory threshold continuously throughout each therapy session. The control group received no vibration. Motor improvement following therapy was quantified as change in the Box and Block Test (ΔBBT) from baseline (pre-therapy) to post-therapy. Post-therapy BBT assessment was performed on average 6 (SD=3.6) days after the last therapy day.

2.3 EEG and MRI Acquisition

EEG was recorded at baseline. A 96-channel active electrode system (actiCAP, BrainAmp MR plus, and Brain Vision Recorder software, Brain Vision LLC, Morrisville, NC) was used. The position of the electrodes followed the international 10-20 system with a ground at AFz and an average reference at FCz. The EEG cap was fitted to the subject's head so that the Cz electrode was positioned at the vertex. The electrode sites were hydrated using SuperVisc gel (Brain Products GmbH, Gilching, Germany) so that the impedance was below 25 kOhms. EEG signals were amplified, bandwidth filtered at 0.10-200 Hz and recorded at 1 kHz.

During EEG, participants were seated comfortably and performed a grip task with the paretic hand. The task was a grip-and-relax sequence, comprised of a 2-sec-long grip and 5-6 sec rest, which was repeated 100 times, similarly with the previous literature.[17] A screen directly in front of the participants displayed visual cues through a custom LabVIEW program (National Instruments, Austin, TX, Figure 1). Upon grip cue, Participants gripped force sensors (Mini40, ATI Industrial Automation Inc., Apex, NC) using the thumb and index finger (Figure 1).

Participants were given a 4 N target amount of force, which resembles the strength required to perform daily activities. Participants practiced the grip-and-relax sequence prior to recording to ensure they understood the instructions. Participants wore ear plugs during EEG recording to reduce influence of outside noise.

To enable lesion-specific source modeling,[14] a structural T1-weighted brain MRI scan with an isometric 1 mm^3 voxel size was obtained via the MPRAGE sequence[18] using a Siemens 3T TIM Trio MRI scanner (Siemens AG, Munich, Germany). Brain MRI was obtained for 10 participants. The other 2 participants had contraindications to MRI.

2.4 EEG and MRI Analysis

The EEG data were preprocessed using MATLAB (The MathWorks, Natick, MA) and EEGLAB toolbox.[19] To remove drifts and line noise, the data were band-pass filtered at 0.5-50 Hz. Bad channels were replaced using spherical interpolation. Independent component analysis was performed, and artifacts were removed using the ADJUST algorithm.[20] Segments with noisy data and no grip were identified from visual inspection of the EEG and force sensor data, respectively, and excluded from further analysis, leaving mean±SD=87±18 grip trials across all participants. Data were then segmented into epochs ranging from -2 to 4.5 sec relative to the grip cue onset.

For source modeling, brain MRI was prepared in the following way. Cortical surfaces were reconstructed and brain regions were segmented using FreeSurfer.[21] The reconstructed and segmented cortical surfaces were then imported into Brainstorm[22] and registered with landmarks (i.e., nasion, right/left auricular, inion, midline, anterior/posterior commissures). Segmentation in the Desikan-Killiany atlas[23] was visually inspected and shown to be incorrect for 5 participants due to large lesions. Thus, segmentation for the regions of interest were

manually drawn for these participants. For 2 participants with contraindication to MRI, the Montreal Neurological Institute average brain[24] was used.

The preprocessed EEG data were imported and co-registered in Brainstorm. A custom forward head model was created for each participant using the Symmetric Boundary Element Method.[25] EEG data was projected to the head model, and source activity was computed using the minimum norm estimation.[26]

Connectivity within the sensorimotor network was quantified using imaginary coherence in Brainstorm.[27] Specifically, the regions of interest were primary motor (M1), premotor, and primary somatosensory (S1) cortices of the sensorimotor network.[28] Ipsilesional sensorimotor connectivity was the primary variable for the hypothesis testing, because ipsilesional hemisphere function is associated with post-stroke UE motor recovery.[8,9,11,12] Connectivity among the 3 regions of interest within a hemisphere were strongly correlated ($r \geq 0.73$). Thus, ipsilesional sensorimotor connectivity was quantified as an average coherence among M1, premotor, and S1 within the ipsilesional hemisphere. As negative control, contralesional and interhemispheric sensorimotor connectivity were also quantified as the average connectivity among the regions of interest within the contralesional hemisphere and between the hemispheres, respectively. The alpha (8-12 Hz) and beta (13-29 Hz) bands were examined because the sensorimotor system has dominant rhythms that peak in the alpha[29,30] and beta bands[31-33] in the brain. Connectivity was obtained for grip preparation (1-sec period immediately prior to the grip cue) and grip initiation (1-sec period immediately after the grip cue onset, as grip occurred at mean±SD=0.7±0.2 sec across all participants based on the force sensor data). Connectivity during the grip preparation phase was used for primary hypothesis testing because the preparation phase is associated with the planning of difficult movements,[34,35] such as precision pinch grip in stroke survivors.

To enable additional comparison with a conventional predictor of lesion volume, lesion volume was extracted by manually drawing the lesion on each participant's individual T1-weighted MRI scan in MRIcron.[36] The stroke lesion maps were normalized into standard space. Lesion locations for the 10 participants with MRI are summarized in Figure 2. Stroke lesion volume was computed as the number of lesioned voxels in cubic millimeters.[37]

2.5 Statistical Analysis

For the primary analysis, the association between ipsilesional sensorimotor alpha/beta connectivity during grip preparation and change in UE motor score post rehabilitation treatment (∆BBT) was examined using regression. Regression also included the between-participant factor of group (treatment vs. control) and the interaction between connectivity and group.

For secondary analysis, the same regression model was applied including other covariates, namely, greater ipsilesional alpha connectivity during grip initiation, contralesional/interhemispheric sensorimotor connectivity, and conventional predictors, including initial function (i.e., BBT score at baseline), age, time-post stroke, and lesion volume, as a predictor for ∆BBT. All statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA).

3. Results

Greater ipsilesional alpha connectivity during grip preparation pre-intervention was associated with greater UE motor improvement following therapy ($p=0.016$, Figure 3A). Group ($p=0.241$) and interaction ($p=0.181$) were not significant. Ipsilesional beta connectivity during grip preparation was not significant ($p=0.507$).

Secondary analysis showed that greater ipsilesional alpha connectivity during grip initiation pre-intervention was also associated with greater UE motor improvement following therapy ($p=0.049$, Figure 3B). Group ($p=0.656$) and interaction ($p=0.823$) were not significant. For negative control, ipsilesional beta connectivity during grip initiation, contralesional/ interhemispheric alpha/beta connectivity during grip preparation/initiation, and conventional predictors (i.e., initial BBT score, age, time-post stroke, lesion volumes) were not associated with UE motor improvement following therapy ($p>0.182$).

4. Discussion

This study investigated whether sensorimotor connectivity assessed with patient-specific EEG source modeling predicts UE motor improvement following task practice therapy with or without subthreshold vibratory stimulation in chronic stroke. Greater ipsilesional alpha connectivity at baseline was found to be associated with greater UE motor improvement following both treatments. Consistent with the literature, conventional predictors[4] and contralesional/interhemispheric alpha/beta connectivity[9,10] were not associated with UE motor improvement following therapy.

Ipsilesional alpha connectivity pre-intervention may represent the extent of the brain's readiness for UE motor therapy and propensity for motor improvement.[38] The sensorimotor network has been shown to have dominant alpha rhythms.[29,30] Alpha oscillatory activity assists in the anticipation of upcoming sensorimotor information by activating necessary brain areas while inhibiting other brain areas that are not needed for the given task.[39] In addition, studies have shown that alpha rhythms are implicated in internal tasks, working memory, and attention.[40-42] This evidence suggests alpha's active role in the fundamental cognitive operations[43] that underlie the performance of motor tasks during therapy. As a result, higher

alpha connectivity is associated with greater motor function in chronic stroke surviors.[44] Furthermore, alpha connectivity assessed using magnetoencephalography (MEG) has been shown to be linked to change in UE motor function after standard rehabilitation in stroke survivors.[38] Based on this evidence, alpha connectivity has been targeted for neurofeedback-based modulation to enhance effectiveness of subsequent UE motor training and maximize UE motor function.[45,46] In summary, there is evidence to suggest, stroke survivors with higher ipsilesional alpha connectivity have the capability of allocating brain resources for paretic UE movement during therapy, thus resulting in greater potential for improving their motor function.

The positive association between ipsilesional alpha sensorimotor connectivity and motor improvement did not differ between the two groups. No significant interaction between group and connectivity indicates the prognostic utility of ipsilesional sensorimotor connectivity for both treatments examined, and possibly for other types of rehabilitation treatments.

Prognosis may not be fixed per pre-intervention connectivity level; however, it could be altered due to treatments. Specifically, motor improvements that surpassed the minimum detectable change (5.5 for BBT)[47] were observed only in stroke survivors with high ipsilesional alpha sensorimotor connectivity in the treatment group that received subthreshold vibratory stimulation. A meta-analysis shows using sensory stimulation in combination with UE rehabilitation treatment enhances motor recovery.[48] Likewise, in the previous pilot randomized controlled trial for the same cohort of participants as in the present study, greater motor improvement was observed for the treatment group using the subthreshold vibratory stimulation than for the control group.[15] Sensory stimulation has been shown to increase sensorimotor network connectivity[49] and enhance associated motor activation[17] via direct neuronal projections from the sensory to motor areas of the brain.[50,51] Thus, motor improvement for a patient of a given connectivity level may not be fixed but could be altered by adding peripheral sensory stimulation or other treatments. Also, note that the 2-week rehabilitation treatment was likely too

short to result in a large motor improvement and longer treatment durations may have resulted in greater change in motor function.[15]

As hypothesized, ipsilesional alpha sensorimotor connectivity during the grip preparation phase was found to be associated with UE motor improvement following therapy. This finding is consistent with the literature that suggests a functional role of connectivity increase during the pre-movement phase of a task[34,35] that is likely attributed to the brain's development of a motor plan.[34] In addition, ipsilesional alpha sensorimotor connectivity during grip *initiation* was associated with UE motor improvement following therapy. Connectivity during grip initiation may be related to the processes needed to execute the motor plan.[34] Thus, sensorimotor connectivity during both the grip preparation and initiation phases may hold prognostic utility for UE motor improvement and should be considered for prediction.

The present study found prognostic potential for alpha connectivity, and not beta. This finding is consistent with the previous MEG study.[38] However, this finding differs from previous EEG studies that found UE prognostic potential for beta[8-13] and not alpha.[9,10,12,13] This difference in findings may be explained by the following. (1) Previous studies investigated subacute (1 week-6 months post-stroke)[8,9] stroke survivors only and/or subacute and chronic combined,[10,11] whereas the present study examined only chronic stroke survivors. Brain rhythms associated with recovery may change over time post stroke, since the beta and theta frequencies are dominant early after stroke,[9] while alpha frequency is dominant in chronic stroke.[38,44] In addition, the inclusion of subacute stroke survivors may have introduced the confounding factor of spontaneous recovery.[52] (2) Previous studies used channel-level EEG analysis[11-13] or source modeling without taking the participant's individual lesion into account.[9,10] In contrast, the present study performed lesion-specific source modeling. (3) All previous studies in chronic stroke[10-13] as well as the present study consist of pilot studies with small sample sizes warranting caution in interpretation and generalizability.

Limitations

The primary limitation is the small sample size. However, there was adequate power to show EEG-based ipsilesional alpha connectivity is a statistically significant predictor of post-stroke UE motor improvement following therapy. These results encourage a larger study to confirm the prognostic utility of connectivity using patient-specific EEG source modeling in post-stroke recovery.

5. Conclusion

This study examined the prognostic utility of ipsilesional sensorimotor connectivity using patient-specific EEG source modeling for UE motor improvement following therapy in chronic stroke survivors. We found that greater ipsilesional alpha connectivity measured pre-intervention was associated with greater UE motor improvement following task-practice therapy with and without subthreshold vibratory stimulation. Overall, EEG-based ipsilesional sensorimotor connectivity demonstrates potential as a prognostic biomarker and may hold utility in predicting motor improvement from therapy in chronic stroke survivors.

Declaration of Interest Statement

N.J. Seo is an inventor of a patent regarding the investigated subthreshold vibratory stimulation. The other authors report no conflicts of interest.

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Figure 1. Experimental setup for the EEG grip task.

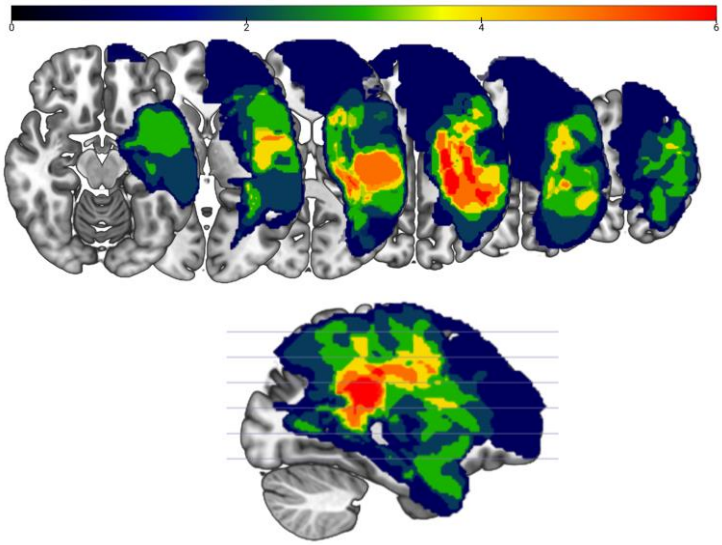
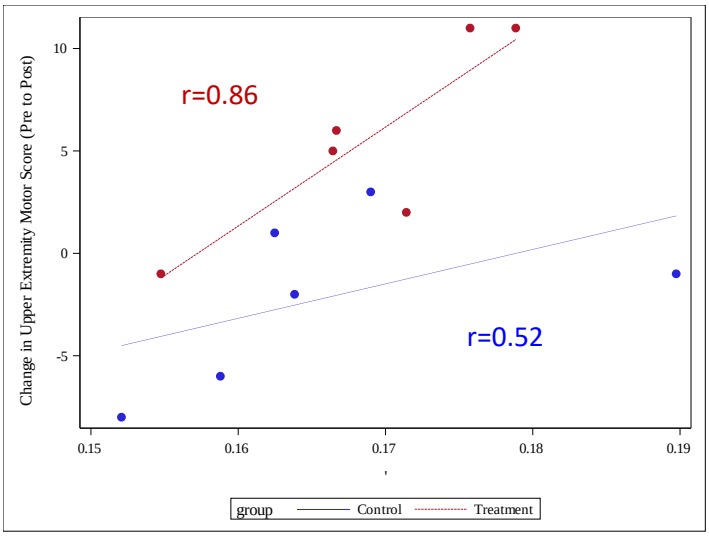
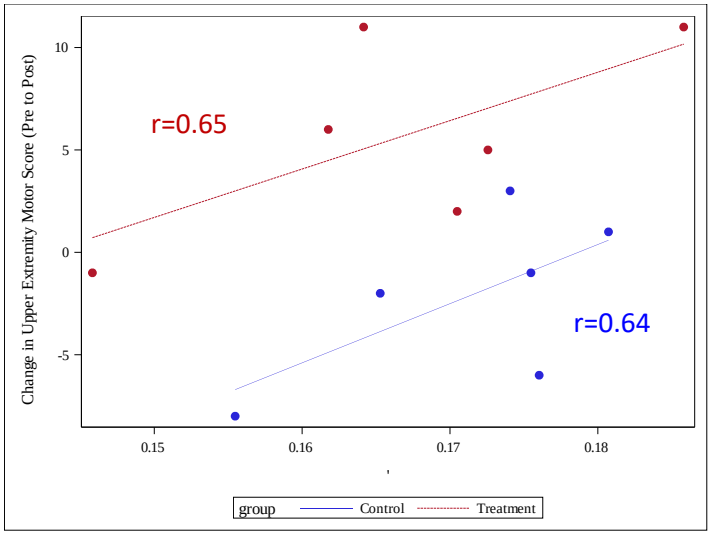


Figure 2. Lesion locations for the 10 participants with an MRI. The color bar shows the number of participants with a lesion at each area (e.g., 6 participants had a lesion in the red colored areas).





(A) **(B)**

Figure 3. (A) Correlation between ipsilesional alpha connectivity during grip preparation and motor improvement (change in upper extremity motor score from pre- to post-intervention). (B) Correlation between ipsilesional alpha connectivity during grip initiation and motor improvement. Solid lines are the fitted regression lines for the control group and dashed lines are for the treatment group.

Chapter 5: Conclusion

These 3 studies were conducted with the overall aim of examining the prognostic utility of EEG in post-stroke UE motor recovery. First, through a systematic review and meta-analysis of the literature, EEG shows potential to predict post-stroke recovery outcomes. Through the implementation of EEG for prognosis in a pilot study with 4 chronic stroke survivors, it is feasible to collect EEG and assess post-stroke UE motor recovery during an UE therapy program. Lastly, through secondary analysis of a pilot randomized controlled trial with 12 chronic stroke survivors, potential prognostic EEG-based biomarkers for UE motor recovery following therapy were identified. Overall, the results of these studies demonstrate the potential for EEG to predict UE motor recovery following therapy in chronic stroke and establish a foundation for further research.

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