ONLINE SUPPLEMENTARY MATERIAL

Electric Field Navigated 1Hz rTMS for Post-Stroke Motor Recovery
The E-FIT Randomized Controlled Trial

Participant enrollment criteria
To be enrolled, candidates for this study had to meet all of the following inclusion criteria and none of the exclusion criteria:

Inclusion Criteria
- ≥ 18 years of age.
- An ischemic stroke suffered 3-12 months prior to the study.
- No other known brain abnormalities by history.
- A one-sided stroke resulting in upper extremity paresis.
- A Chedoke–McMaster Stroke Assessment arm stage and hand stage of 3-6 for the affected limb.

Exclusion Criteria
- Implanted metallic parts of implanted electronic devices, including pacemakers, defibrillators, or implanted medication pumps.
- Pregnant or trying to become pregnant; Lack of pregnancy established in females of child-bearing potential by a negative urine pregnancy test at screening.
- Active alcohol abuse, illicit drug use or drug abuse or significant mental illness.
- Patients suffering from depression as measured by a score of >10 on the Patient Health Questionnaire(PHQ9). For clarity, patients diagnosed with depression controlled with stable anti-depressivemedication and in whom PHQ9 is <10 were eligible to participate in the trial.
- History of epilepsy, defined as at least two unprovoked seizures occurring greater than 24 hours apartor diagnosis of an epilepsy syndrome, and no seizures within the last 12 months.
- Any condition that would prevent the subject from giving voluntary informed consent.
- An implanted brain stimulator.
- Any metal in the head except dental work or any ferromagnetic metal elsewhere in the body.
- Enrolled or plans to enroll in an interventional trial during this study.
- Scalp wounds or infections.
- Claustrophobia precluding MRI.
- A fixed contraction deformity in the affected limb that would prevent normal dexterity if patient wereneurologically intact.
- Excessive spasticity as indicated by the Modified Ashworth Spasticity (MAS) Scale >2/4 in either elbow flexors, wrist flexors or finger flexors of the affected limb; Previous stroke with residual deficits (TIAs not a reason for exclusion).
- Premorbid (retrospective) modified Rankin Scale (mRS) score ≥2 of any etiology.
- A concurrent progressive neurologic disorder, acute coronary syndrome, severe heart disease (NYHAClassification > 3), or other major medical condition.
- Confirmed or suspected lower-limb fracture preventing mobilization.
- Patients requiring palliative care.
- Patients planning to undergo any other occupational therapy during the 6-week active treatment periodof the trial than what is provided in the study.
- A recent injection of botulinum toxin to the affected upper limb in the last 3 months, or the need for an injection of botulinum toxin anytime during the study period and follow-up.
- A recent injection of phenol to the affected upper limb in the last 6 months or the need for an injection of phenol anytime during the study period and follow up.

- Ataxia as measured by a score > 1 on item 7 (limb ataxia) of the NIH stroke scale.
- Severe sensory deficits as measured by a score of 2 on item 8 of the NIH stroke scale.
- Severe aphasia as measured by a score of > 2 on item 9 (best language) of the NIH stroke scale.
- Severe neglect as measured by a score of 2 on item 11 (extinction and inattention) of the NIH strokescale.
- Patients unable to comprehend or follow verbal commands.
- Based on PI's or local physician's assessment patient unable to tolerate the trial procedure due to a medical condition.
- A Mini-mental status exam (MMSE) <25.

Intervention and Instrumentation

Transcranial Magnetic Stimulation

Nexstim Application Specialists provided trial staff training and certification for study device use. The Nexstim Navigated Brain Therapy (NBT) System was used to localize the cortical target for rTMS delivery on the contralesional hemisphere and to deliver rTMS to that location (the same device used in the NICHE trial). The method of use in both trials was identical, with the only difference being the sham coil used. The Nexstim NBS technology provides navigational accuracy for the NBT system. NBS technology is FDA cleared for localization of primary motor cortex [K091457] and language function [K112881]. During the E-FIT trial the technology was FDA cleared to treat major depressive disorder [K171902].
The Nexstim TMS Stimulator was used in the study deliver the rTMS-therapy in 1Hz rTMS mode (biphasic pulse), and the motor cortex mapping to locate the therapy delivery target using single-pulse TMS paradigms.
Motor mapping of the healthy hemisphere was performed to determine the motor threshold and the optimal cortical representation area of m. Extensor Digitorum Communis (m.EDC). rTMS treatment targeted this site during the trial treatment visits. The TMS motor mapping was determined using a 3x3mm grid centered over the hand-knob. The treatment site was the location with the largest MEP amplitude. The resting motor threshold was determined using custom/proprietary software.

Active rTMS
For patients randomized to receive rTMS, the stimulation was delivered in a single pulse train 900 pulses given at 110% of the motor threshold. The motor threshold was determined at each visit. The train was targeted on the motor representation of the m.EDC on the healthy brain hemisphere was determined at the baseline visit (thus, the same location at each visit).

Sham rTMS
For patients randomized to receive Sham rTMS, the sham stimulation was delivered in a single 1Hz pulse train of 900 pulses given using a Sham coil. Sham condition was delivered using the NBT system to navigate and localize a sham TMS coil to the same position on the patient's head as the active TMS coil would have been located if active NBT- rTMS had been delivered. The sham coil was outwardly identical to the active TMS coil and caused similar auditory and sensory scalp responses as the active coil.

Sham coil validation
Prior to EFIT the coil was successfully validated for blinding success in 8 healthy subjects, all of whom had previous experience of having been stimulated with TMS. Validation involved the following: correct identification of the coil used (active/sham); potential difference in the noise level between the 2 coils; and potential difference in tactile sensation caused by the 2 coils.

Motor therapy

The same protocol for arm and hand therapy was used in the E-FIT trial as in the NICHE trial and is described in detail . All study therapists were trained by a single study wide therapy trainer. Therapy focused on arm and hand practice with meaningful functional tasks selected by the patient and therapist and graded for skill level based on participant's current Chedoke hand stage. During the 6 weeks active treatment period (visits 3-20), the patients were not allowed any other occupational therapy except that provided in the trial. After the active treatment period during the 6 month follow-up period of the trial, patients were allowed occupational therapy. The hours of therapy were documented. Patients were queried once every 2 weeks until the final outcome assessment visit at 6 months after the end of active trial treatment, either when they visited the study site or were called and queried.

Physical therapy
Patients were allowed to participate in physical therapy for the full trial duration, including during the active treatment period of the trial (visits 3-20). However, the hours of therapy were documented. Patients were queried once every 2 weeks until the final outcome assessment visit at 6 months after endof active trial treatment, either when they visited the study site or were called and queried.

Home exercise program
During the 6 weeks active treatment period of the trial (visits 3-20) the patients were not allowed an upper limb home exercise program prescribed by therapists other than the study therapist. The study therapist provided an upper limb home exercise program for the active treatment period of the trial. The study therapist also provided an upper limb home exercise program for the post-active treatment period of the trial. However, this home exercise program for the post-active treatment period could be modified by the patient's own therapist based on her/his assessment of the patient's clinical needs. The hours of therapy were documented. Patients were queried once every 2 weeks until the final outcome assessment visit 6 months after the end of active trial treatment, either when they visited the study site or were called and queried.

Statistical Analysis

Safety was assessed in subjects in the safety population. The primary efficacy analysis population wasthe intent-to-treat (ITT) population. In addition, a separate analysis was conducted on the per protocol (PP) population.
Primary Efficacy Analysis
The beneficial effect of 1Hz NBS guided rTMS was established if a statistically significantly greater proportion of patients receiving NBS-rTMS attain clinically importantimprovement in the primary outcome measure (UEFM, 5 points or above) than patients receiving sham-rTMS between baseline and 6 months post-treatment.
The size of the treatment effect was measured by the odds ratio parameter, which is defined as:

$$OR = \frac{P_{TRT}/(1-P_{TRT})}{P_{REF}/(1-P_{REF})}$$

Where P_{TRT} and P_{REF} denote the proportion of subjects with clinically significant change from baseline in Fugl-Meyer score, in the treatment and reference groups, respectively.
The null hypothesis was $H_0 : OR = 1$ and the two-sided alternative hypothesis was $H_1 : OR \neq 1$.
The proportion of responders in each treatment group was summarized, along with the estimatedodds ratio from the Bayesian model and the 96% credible interval of the odds ratio.

For robustness demonstration of the Bayesian primary efficacy analysis, a Mantel-Haenzel Chi-squared test was also performed to analyze the primary endpoint. Only data from the current E-FIT study was used (no data borrowing). The analysis was repeated with and without the stratification variable (time since stroke: 3-6 months or 6-12 months). The analysis was repeated on both ITT and PP populations.

Secondary Efficacy Analyses
Similarly to the primary efficacy analysis, statistical analysis of the secondary outcomes was the performance in two phases. The Bayesian analysis of the E-FIT data combined with data borrowed from the active trial arm of the previously completed NICHE trial was the primary analysis. Non-Bayesian analysis of the E-FIT trial data only was then performed to demonstrate the robustness of the result. See also separate statistical analysis plan.
An absolute improvement (in points) of each of the secondary outcome measures (Fugl-Meyer score, ARAT score, NIHSS score, and EQ-5D score) was analyzed. Descriptive statistics of the scores (as continuous variables) were reported by treatment group and study visit (5-10 days, 1, 3, and 6 months follow-up).
All secondary analyses were performed on the ITT population, and the PP population (for sensitivity).

Primary Safety Analysis
The number of subjects with SAEs and TEAEs was summarized by group and compared using a Chi-Square test.
A p-value of <0.05 was considered significant for all analyses.

Strata and Covariates used in statistical analysis
The primary efficacy analysis was stratified by length of time after stroke (3-6 months vs. 6-12 months). Additional covariate analyses modeled the primary endpoint (a binary response of UEFM score improvement) and the absolute changes (in points) in the tests of motor function (UEFM, ARAT) usinghours of occupational therapy outside the trial and overall hours of therapy (occupational, physical, and home exercise) as covariates during the treatment phase and over the entire 6 months of follow-up.

Missing data values
Missing values for the primary and secondary outcome measures were imputed using Last Observation Carried Forward (LOCF) principle.

Safety population
The safety population consisted of all subjects who received study treatment. Subjects in the safety population were summarized and analyzed according to the treatment they actually received, regardless of whether or not they were randomized to receive that treatment.

Intent-to-treat population
The ITT population consisted of all randomized subjects who participated in the baseline visit. Subjectsin the ITT population were be summarized and analyzed in the treatment group to which they were randomized, regardless of the treatment they actually received.

Per protocol population
The Per-protocol (PP) population consisted of all randomized subjects, received study treatment, and had no major protocol violations.
The following were predefined as major protocol violations:

1) Protocol deviations on inclusion/exclusion criteria
2) Missing more than one full treatment session. If there are partially completed visits, the categorization will be determined on an individual basis by a blinded sponsor representative. Note that subjects were allowed 7 weeks to reach their full 18 session treatment program.
3) Receiving a botulinum toxin (BOTOX) injection(s) in the stroke-affected upper limb.
4) rTMS treatment with a coil other than what should have been used based on the subject's randomization to active /sham group could result in a major or minor

protocol deviation based on the following predefined principles:

a) Minor deviation if a subject randomized to the active group received only one session with a sham coil.
b) Major deviation if a subject randomized to the sham group received one session with an active coil.
c) Major deviation if a subject (active or sham) received more than one session with the wrong coil.
d) If a subject received a partial session with the wrong coil, the cut-off for a session to qualify for a major deviation was defined as 100 pulses. Therefore,
    a. Minor deviation if a sham subject received one partial session (<100 pulses) with an active coil.
    b. Major deviation if a sham subject received one partial session (≥100 pulses) with an active coil.
    c. Minor deviation if an active subject received one partial session (any number of pulses) with a sham coil.
    d. A partial session would have counted towards the total in rule #c) above if it consisted of at least 100 pulses.

Subject populations in the final analysis

Final analysis

The final analysis of E-FIT data alone was performed in three populations:

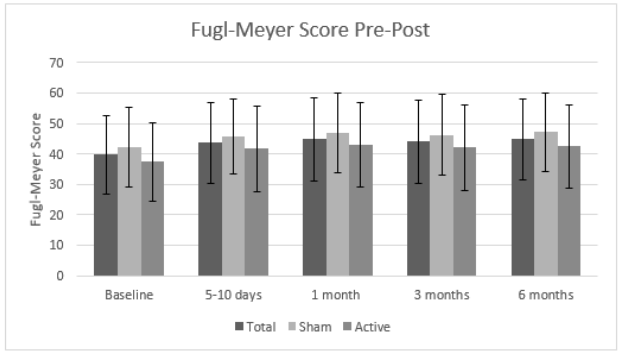
1) Safety population – all 58 subjects were randomized and receiving treatment, 30 in the active and 28 in the sham trial arm.
2) Intent-to-treat (ITT) population – all 58 subjects randomized who participated in the baseline visit (Note: of the 60 patients enrolled in the trial, 2 withdrew consent before participating in the baseline visit), 30 in the active and 28 in the sham trial arm.
3) Per protocol (PP) population – ITT population resulted in 10 subjects with major protocol deviations excluded. The final per protocol population comprised 50 subjects - 25 in the active and 25 in the sham group.

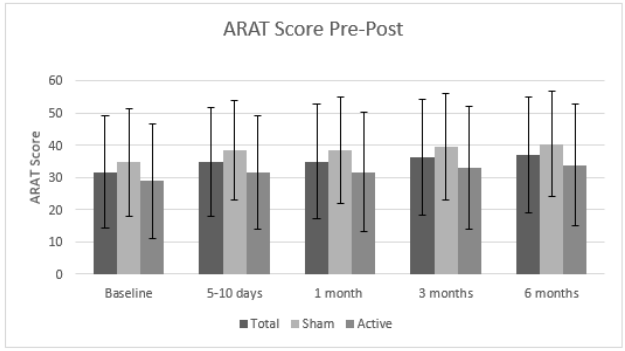
The final analysis of E-FIT data combined with data borrowed from NICHE trial was performed in the threepopulations defined for E-FIT above combined with NICHE data of the corresponding population but limited to data from subjects with ischemic stroke in the active trial arm.

Results

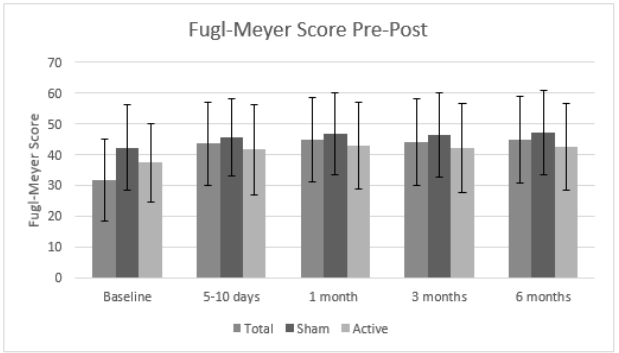
Figure S1. Motor performance pre-post treatment A. Intent-to-treat population B. Per-protocol population

A. Intent-to-treat population





B. Per-protocol population



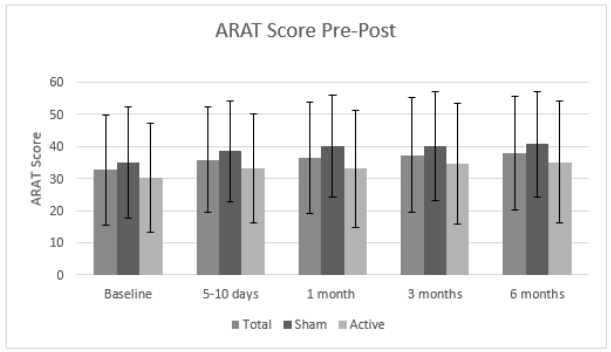
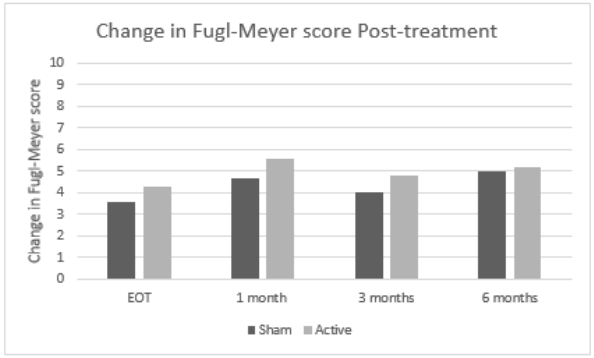
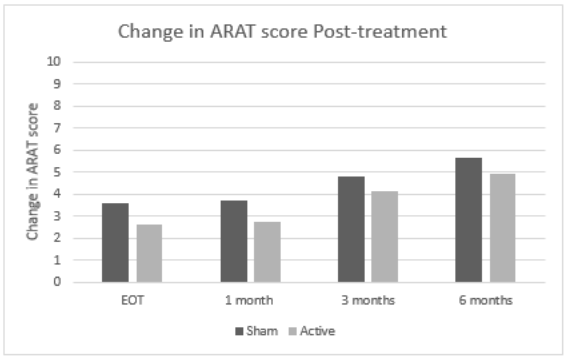


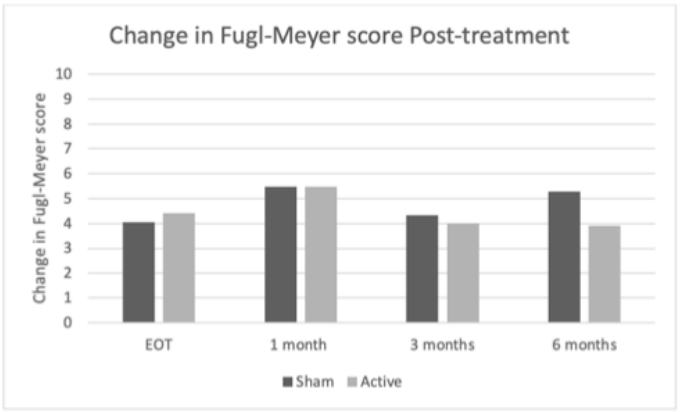
Figure S2. Change in motor performance pre-post treatment A. Intent-to-treat population B. Per-protocol population

A. Intent-to-treat population





B. Per-protocol population



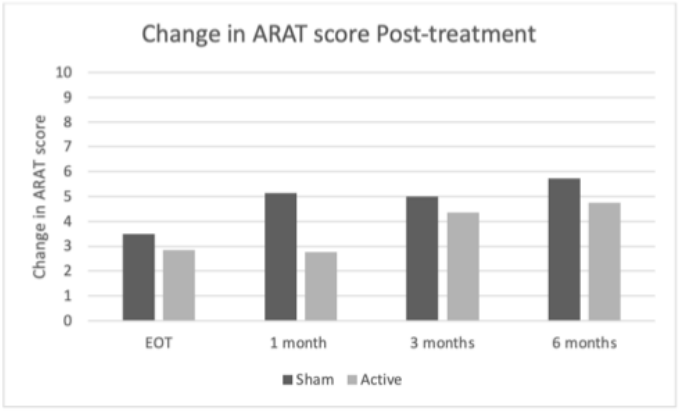


Table S1: Secondary Outcome Measures: Fugl-Meyer scores and Action Research Arm Test Scores

A. Intent to treat population						
	Fugl-Meyer Scores			Action Research Arm Test Scores		
	Total	Sham	Active	Total	Sham	Active
Baseline	39.71 (13.07)	42.21 (13.18)	37.37 (12.74)	31.67 (17.33)	42.21 (13.18)	37.37 (12.74)
5-10 days	43.64 (13.27)	45.75 (12.18)	41.67 (14.13)	43.64 (13.27)	45.75 (12.18)	41.67 (14.13)
1 month	44.84 (13.54)	46.89 (13.14)	42.93 (13.85)	44.84 (13.54)	46.89 (13.14)	42.93 (13.85)
3 months	44.12 (13.67)	46.25 (13.22)	42.13 (14.01)	44.12 (13.67)	46.25 (13.22)	42.13 (14.01)
6 months	44.79 (13.44)	47.21 (12.98)	42.53 (13.69)	44.79 (13.44)	47.21 (12.98)	42.53 (13.69)
B. Per Protocol population						
	Fugl-Meyer Scores			Action Research Arm Test Scores		
	Total	Sham	Active	Total	Sham	Active
Baseline	40.22 (13.33)	42.24 (13.87)	38.20 (12.72)	32.64 (17.25)	35.04 (17.43)	30.24 (17.08)
5-10 days	44.44 (13.57)	46.28 (12.47)	42.60 (14.61)	35.80 (16.38)	38.52 (15.70)	33.08 (16.92)
1 month	45.65 (13.66)	47.71 (13.34)	43.68 (13.95)	36.51 (17.34)	40.17 (15.85)	33.00 (18.29)
3 months	44.38 (14.12)	46.56 (13.71)	42.20 (14.47)	37.32 (17.93)	40.04 (16.95)	34.60 (18.81)
6 months	44.82 (14.05)	47.52 (13.58)	42.12 (14.26)	37.88 (17.82)	40.76 (16.46)	35.00 (18.99)

Table S2: Secondary Outcome Measures: NIHSS and EQ-5D VAS

A. Intent to treat population						
	Fugl-Meyer Scores			Action Research Arm Test Scores		
	Total	Sham	Active	Total	Sham	Active
Baseline	39.71 (13.07)	42.21 (13.18)	37.37 (12.74)	31.67 (17.33)	42.21 (13.18)	37.37 (12.74)
5-10 days	43.64 (13.27)	45.75 (12.18)	41.67 (14.13)	43.64 (13.27)	45.75 (12.18)	41.67 (14.13)
1 month	44.84 (13.54)	46.89 (13.14)	42.93 (13.85)	44.84 (13.54)	46.89 (13.14)	42.93 (13.85)
3 months	44.12 (13.67)	46.25 (13.22)	42.13 (14.01)	44.12 (13.67)	46.25 (13.22)	42.13 (14.01)
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B. Per Protocol population						
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Baseline	40.22 (13.33)	42.24 (13.87)	38.20 (12.72)	32.64 (17.25)	35.04 (17.43)	30.24 (17.08)
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6 months	44.82 (14.05)	47.52 (13.58)	42.12 (14.26)	37.88 (17.82)	40.76 (16.46)	35.00 (18.99)

Table S3: Blinding effectiveness

A. Comparison of actual randomization to subjects' belief of randomization			
Subject's opinion	Actual Treatment Received		Chi-Square p-value
	Sham N=28	Active N=27	
Active	18 (64%)	15 (56%)	0.5088
Sham	10 (36%)	12 (44%)	
B. Comparison of actual randomization to assessors' belief of randomization			
Assessor's opinion	Actual Treatment Received		
	Sham	Active	
First follow-up (5-10 days after treatment)			
Sham	2 (7.1%)	2 (7.1%)	
Active	1 (3.6%)	3 (10.7%)	
Don't know	25 (89.3%)	23 (82.1%)	
Last follow-up (6 months after treatment)			
Sham	1 (3.6%)	4 (14.3%)	
Active	4 (14.3%)	1 (3.6%)	
Don't know	23 (82.1%)	23 (82.1%)	