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Changes in Upper-Limb Function and Activities of Daily Living After High-Frequency Repetitive Transcranial Magnetic Stimulation and Rehabilitation in Patients Aged 80 Years or Older with Subacute Stroke: A Retrospective Observational Study

Ryota Nakamura [1], Masachika Niimi [2,*], Moe Fujita [1], Wataru Nukii [1,2,3], Takahiro Fukazawa [1,2], Reo Tsuchida [1], Ryo Kasama [1], Yu Miida [1], Yuzumi Oda [1], Chikashi Fukaya [1,2,4] and Takamitsu Yamamoto [1,5]

[1] Department of Rehabilitation, Sonodakai Neurorehabilitation Hospital, 1-10-10 Aoi, Adachi-ku, Tokyo 120-0012, Japan
[2] Department of Rehabilitation Medicine, Nihon University School of Medicine, 30-1, Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan
[3] Department of Rehabilitation Medicine, Nihon University Graduate School of Medicine, 30-1, Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan
[4] Department of Neurological Surgery, Nihon University School of Medicine, 30-1, Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan
[5] Neuromodulation Center, Sonodakai Neurorehabilitation Hospital, 1-10-10 Aoi, Adachi-ku, Tokyo 120-0012, Japan
* Correspondence: pomardon2010@gmail.com

Abstract

Background/Objectives: Evidence for high-frequency repetitive transcranial magnetic stimulation (rTMS) in patients aged 80 years or older after stroke remains limited. We examined functional changes during rTMS combined with rehabilitation. **Methods:** This single-center retrospective study included 18 patients treated 1–3 months after stroke onset during 2019–2025. The first 4 weeks of ipsilesional 10 Hz rTMS combined with rehabilitation were analyzed. Fugl-Meyer Assessment of the Upper Extremity (FMA-UE) scores at admission, at rTMS initiation, and 2 and 4 weeks after rTMS initiation were analyzed using linear mixed-effects models. Secondary outcomes were Wolf Motor Function Test time (WMFT-Time), Functional Ability Scale (WMFT-FAS), and Functional Independence Measure motor scores (FIM-motor). These were compared using exact two-sided Wilcoxon signed-rank tests; WMFT-Time was natural log-transformed. Holm adjustment was applied separately to six FMA-UE contrasts and three secondary outcomes. **Results:** FMA-UE scores increased by an estimated 13.44 points from rTMS initiation to 4 weeks after initiation (95% confidence interval [CI], 10.35–16.54; Holm-adjusted $p < 0.001$). An exploratory piecewise model estimated a higher improvement rate after rTMS initiation than before initiation (difference, 0.251 points/day; 95% CI, 0.072–0.430; unadjusted $p = 0.007$). Median values changed from 12.00 to 4.36 s for WMFT-Time, 3.10 to 3.77 for WMFT-FAS, and 41.50 to 57.50 for FIM-motor (all Holm-adjusted $p < 0.001$). No serious rTMS-related adverse events were documented among analyzed patients. **Conclusions:** In this retrospective, uncontrolled study, upper-limb function and activities of daily living improved during high-frequency rTMS combined with rehabilitation in patients aged 80 years or older with subacute stroke.

Keywords: subacute stroke; repetitive transcranial magnetic stimulation; rehabilitation; aged; 80 and over; upper-limb function; activities of daily living

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Academic Editor: Jinyuan Zhou

Received: 5 October 2026
Revised: 19 November 2026
Accepted: 26 November 2026
Published: 28 November 2026

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1. Introduction

Stroke is a leading cause of disability worldwide [1], and limb motor impairment is common in the acute phase [2]. Upper-limb impairment limits the ability to perform activities of daily living (ADL) and substantially affects patients' independence and quality of life [3]. Stroke incidence increases with age, and population aging is projected to contribute to an increase in the number of older adults living with stroke in the European Union [4,5]. A shift toward older ages at stroke onset has also been reported in Japan [6]. These demographic changes underscore the need for effective rehabilitation strategies to promote functional recovery in patients aged 80 years or older after stroke.

Neuroplasticity, particularly within the cerebral cortex, plays an important role in upper-limb functional recovery after stroke [7,8]. High-frequency repetitive transcranial magnetic stimulation (rTMS), which modulates cortical excitability, has been reported to improve upper-limb motor function [9,10]. Initial upper-limb impairment and function are important predictors of recovery, whereas evidence regarding the prognostic value of age has been inconsistent [11]. In patients with first-ever ischemic stroke, older age at stroke onset has been associated with lower odds of attaining the maximum upper extremity Fugl-Meyer Assessment score at 6 months after stroke [12]. In Predict Recovery Potential 2 (PREP2), patients with a Shoulder Abduction and Finger Extension (SAFE) score of at least 5 within 72 h after stroke are stratified by age. Patients younger than 80 years are predicted to have an Excellent upper-limb outcome at 3 months, whereas patients aged 80 years or older require a SAFE score of at least 8 for this predicted category [13].

Age-related alterations in the response to noninvasive brain stimulation have been reported in healthy adults. Paired associative stimulation produced increases in motor cortical excitability in younger groups, with attenuated responses at older ages [14]. Similarly, excitability enhancement after anodal transcranial direct current stimulation was reduced in older adults [15]. These observations suggest that aging may influence stimulation-induced plasticity.

Age-related changes have also been observed in plasticity associated with motor learning. In healthy adults, motor practice induced smaller training-dependent changes in motor cortical representations with increasing age, despite comparable movement kinematics during training [16]. Taken together, these findings suggest that aging may attenuate some forms of neuroplasticity induced by noninvasive brain stimulation and motor practice. It is therefore important to examine functional outcomes during combined rTMS and rehabilitation in older patients with stroke.

However, evidence regarding high-frequency rTMS in patients aged 80 years or older remains limited. A previous study of high-frequency rTMS in subacute ischemic stroke excluded patients older than 80 years at admission [17]. This exploratory retrospective study examined the hypothesis that upper-limb motor function and ADL independence would improve over 4 weeks during high-frequency rTMS combined with rehabilitation in patients aged 80 years or older with subacute stroke.

2. Materials and Methods

2.1. Study Design and Participants

This retrospective observational study included patients with post-stroke hemiparesis who were admitted to Sonodakai Neurorehabilitation Hospital between January 2019 and December 2025 and received rehabilitation and high-frequency rTMS as part of routine clinical care. The observation period began in 2019 because rTMS was introduced into routine clinical practice at our hospital that year. In routine clinical practice, rTMS was provided to adults aged 18 years or older, including patients aged 18–79 years. The present

study selected only patients aged 80 years or older. Patients were identified from medical records and rehabilitation assessment records.

Patients were eligible for inclusion if they met all of the following criteria:

1. Age of 80 years or older, with hemiparesis following a first-ever ischemic or hemorrhagic stroke;
2. Initiation of high-frequency rTMS 1–3 months after stroke onset, within the early subacute phase [18];
3. Availability of assessments at rTMS initiation and 4 weeks after initiation;
4. Continued participation in conventional rehabilitation.

Patients were excluded if they met any of the following criteria:

1. Recurrent stroke during the assessment period;
2. Deterioration in medical condition that prevented continuation of rehabilitation or rTMS during the assessment period;
3. Insufficient documentation to verify rTMS parameters, assessment timing, or assessment content.

The following clinical criteria were used to determine eligibility for rTMS treatment in routine practice at our hospital and were not established specifically for this study. High-frequency rTMS was offered to adults with upper-limb Brunnstrom recovery stages II–V. Stage II involves emerging spasticity and minimal synergistic movements; stage III, voluntary movement predominantly within synergies; stage IV, some movements outside synergies; and stage V, more complex movements with reduced dependence on synergies [19]. These patients had residual paresis and impaired selective motor control, which were the targets of rTMS combined with rehabilitation tailored to their motor ability. Previous rTMS studies have included patients with upper-limb stages II–V [20] or hand-finger stages III–V [21].

Patients were not eligible for treatment if they had intracranial metal; implanted medical devices, such as cardiac pacemakers; a history of epilepsy or unexplained seizures; severe cardiac disease; a Mini-Mental State Examination (MMSE) score below 24 [22]; psychiatric disorders; cognitive impairment that precluded assessment; sleep deprivation; or alcohol dependence. Patients with neuroimaging evidence of intracranial lesions associated with an increased risk of seizures, or with other central nervous system disorders, were also ineligible. Routine clinical selection also excluded patients with cerebellar involvement, impaired consciousness preventing informed consent, or inability to complete the MMSE because of aphasia.

Age, sex, stroke type, side of paresis, upper-limb Brunnstrom recovery stage at rTMS initiation, and the intervals from stroke onset and hospital admission to rTMS initiation were extracted from medical records.

2.2. Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects in Japan. The Sonodakai Institutional Review Board specifically approved the present retrospective observational study examining changes in upper-limb function and ADL during rTMS combined with rehabilitation in patients aged 80 years or older with subacute stroke (No. 225; approved on 29 September 2026).

This retrospective study used information collected during clinical care. Study information was posted within the hospital, and patients were given an opportunity to opt out of participation. Data were anonymized for analysis and handled in a manner that prevented individual identification.

Written and verbal consent for rTMS treatment was obtained separately from the research opt-out procedure.

2.3. High-Frequency rTMS and Rehabilitation Protocol

High-frequency rTMS was delivered using a MagPro R30 magnetic stimulator and a cooled coil (Cool D-B80; both manufactured by MagVenture, Farum, Denmark).

During rTMS, patients were seated in a chair or wheelchair. A pillow was used to support the neck and head, and the operator provided additional manual support to minimize head movement.

Stimulation targeted the upper-limb and hand representation of the ipsilesional primary motor cortex (M1). The resting motor threshold (rMT) was defined as the lowest single-pulse transcranial magnetic stimulation (TMS) intensity that elicited motor evoked potentials (MEPs) with an amplitude of at least 50 μV in the paretic abductor pollicis brevis (APB) muscle at rest in at least 5 of 10 trials. The rTMS intensity was set at 90% of rMT.

Under our institutional clinical protocol, single-pulse TMS for rMT determination was limited to 60% of maximum stimulator output (MSO). A previous study using a double-cone coil also applied a 60% MSO upper limit during motor threshold determination [23]. This was an operational ceiling for the clinical protocol, rather than a universal upper limit for rMT determination. When the rMT criterion could not be met at or below this intensity, rMT was classified as not determined within the tested intensity range. In these patients, rTMS was delivered at a fixed intensity of 54% MSO, corresponding to 90% of the 60% output level. Intensities above 60% MSO were not tested.

The same rTMS protocol was used for all patients. Stimulation was delivered at 10 Hz in 10 s trains containing 100 pulses, with a 15 s interval between trains. Each session comprised 10 trains, for a total of 1000 pulses. Sessions were scheduled 6 days per week, excluding Sundays. The first 4 weeks after rTMS initiation were defined as the analysis period, corresponding to a planned total of 24 sessions and 24,000 pulses during this period.

Patients received a total of 3 h of rehabilitation daily. On rTMS treatment days, approximately 1 h was devoted to upper-limb and hand rehabilitation after stimulation. The remaining approximately 2 h focused on ADL training and rehabilitation targeting lower limb function. Upper-limb and hand rehabilitation included range-of-motion exercises, repetitive upper-limb and finger movements, pegboard tasks, object manipulation, and electrical stimulation therapy. Task difficulty was adjusted to each patient's motor function. The duration of upper-limb and hand rehabilitation was broadly comparable across patients. Rehabilitation was also provided on Sundays.

High-frequency rTMS was administered with a physician present.

2.4. Outcome Measures

2.4.1. Fugl-Meyer Assessment of the Upper Extremity

The primary outcome was upper-limb motor impairment, assessed using the Fugl-Meyer Assessment of the Upper Extremity (FMA-UE). This assessment covers proximal and distal motor function, movements within and outside synergy patterns, reflex activity, and coordination and speed [24,25].

The FMA-UE comprises 33 items assessing the shoulder, elbow, forearm, wrist, hand, coordination and speed, and reflexes. Items are scored from 0 to 2 according to standardized criteria, yielding a total score of 0–66, with higher scores indicating better motor function [24]. The assessment has demonstrated intrarater and interrater reliability and validity in patients with stroke [25,26].

2.4.2. Wolf Motor Function Test

The Wolf Motor Function Test (WMFT) was used to assess functional task performance and movement quality of the paretic upper limb [27]. The WMFT evaluates upper-limb performance during tasks relevant to everyday activities, and its reliability and validity have been reported in patients with stroke [28,29]. It comprises 15 functional tasks and 2 strength tasks. The 15 functional tasks [29] were assessed in this study using task completion time (WMFT-Time) and the Functional Ability Scale (WMFT-FAS).

For WMFT-Time, the time required to complete each task was recorded. The maximum time allowed was 120 s per task, and tasks that were not completed within this limit were assigned a value of 120 s. WMFT-Time was defined as the arithmetic mean completion time across the 15 tasks for each patient at each assessment. To account for skewness, this mean time was natural log-transformed before statistical testing [30]. Descriptive statistics for WMFT-Time and its within-patient change were calculated on the original scale and are presented in seconds as medians (first–third quartiles). WMFT-Time was plotted in seconds on a linear scale.

For WMFT-FAS, movement quality was rated on a six-level ordinal scale, ranging from 0 (no attempt to use the paretic upper limb) to 5 (movement appears normal). The mean score across the 15 tasks was calculated.

2.4.3. Functional Independence Measure

The Functional Independence Measure (FIM) was used to assess independence in ADL [31,32]. The FIM comprises 18 items across six domains: self-care, sphincter control, transfers, locomotion, communication, and social cognition. Each item is rated on a seven-level ordinal scale according to the amount of assistance required, from 1 (total assistance) to 7 (complete independence). Total scores range from 18 to 126, with higher scores indicating greater independence.

The motor subscale (FIM-motor) was calculated to assess the motor domains of functional independence. FIM-motor comprises 13 items covering self-care, sphincter control, transfers, and locomotion, with a total score ranging from 13 to 91 [33]. FIM-motor was analyzed as a secondary outcome.

2.5. Assessment Schedule

FMA-UE was assessed at four time points: admission (T0, at a patient-specific interval before rTMS initiation), rTMS initiation (T1, day 0), 2 weeks after initiation (T2, days 14–15), and 4 weeks after initiation (T3, days 28–30). WMFT-Time, WMFT-FAS, and FIM-motor were assessed at T1 and T3. Assessment data and timing were extracted retrospectively from clinical records. All outcome assessments were performed as part of routine clinical care by assessors who were not blinded to rTMS treatment.

2.6. Statistical Analysis

Changes in FMA-UE scores over time were analyzed using a linear mixed-effects model with assessment time point as a categorical fixed effect and a participant-specific random intercept. The primary comparison was between rTMS initiation and 4 weeks after initiation, and Holm adjustment was applied to all six pairwise comparisons among the four assessment time points. The five additional comparisons were examined during manuscript revision and interpreted as exploratory.

As an exploratory post hoc analysis, we counted patients whose FMA-UE scores increased by at least 9 points and by at least 10 points from rTMS initiation to 4 weeks. These thresholds were based on published minimal clinically important difference (MCID) estimates in patients with subacute stroke: 9 points anchored to the modified Rankin scale

and 10 points anchored to patient-perceived change [34]. Both thresholds were applied to describe clinically meaningful improvement, although their validity was not assessed specifically in the present cohort.

WMFT-Time, WMFT-FAS, and FIM-motor at rTMS initiation and 4 weeks after initiation were compared using exact two-sided Wilcoxon signed-rank tests, with Holm adjustment across the three outcomes. WMFT-Time was natural log-transformed before analysis. For all Wilcoxon tests, tied absolute differences received average ranks, and zero differences were excluded before ranking. Effect sizes were calculated as $r = |Z|/\sqrt{N}$, where Z is the standardized signed-rank statistic without continuity correction, and N is the number of participants with complete paired data.

Rates of FMA-UE improvement before and after rTMS initiation were compared using a continuous piecewise linear mixed-effects model with a knot at initiation and participant-specific random intercepts. Time was expressed in days relative to initiation, using each participant's actual admission-to-initiation interval before initiation and nominal days 14 and 28 afterward. A supplementary exact two-sided Wilcoxon signed-rank test compared FMA-UE scores at rTMS initiation and 4 weeks after initiation. The *p* values for the slope-difference test and the supplementary Wilcoxon test were unadjusted and interpreted as exploratory.

Both mixed-effects models were fitted by restricted maximum likelihood, with Kenward–Roger inference. Reported 95% confidence intervals (CI) were pointwise intervals without multiplicity adjustment. No missing-value imputation was performed. All tests were two-sided, with a significance level of 0.05. For analyses with Holm adjustment, statistical significance was assessed using adjusted *p* values. Statistical analyses were performed using R version 4.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

ChatGPT (version: GPT-6 Astra; OpenAI, San Francisco, CA, USA) was used to assist with English translation, language editing, and code generation for statistical analysis and figure preparation; details are provided in the Acknowledgments.

3. Results

3.1. Participants and Treatment Completion

Among 263 admission records for patients aged 80 years or older screened between January 2019 and December 2025, 19 readmissions and eight records with diagnoses other than cerebral infarction or intracerebral hemorrhage were excluded, leaving 236 patients. Of these, 208 were not selected for rTMS under routine clinical criteria. Twenty-eight patients (11.9%) met the clinical eligibility criteria for rTMS, of whom seven were transferred before treatment initiation. Twenty-one patients received rTMS. Three were excluded from this retrospective study because of recurrent stroke ($n = 1$), deterioration in medical condition ($n = 1$), or assessment data that could not be verified ($n = 1$), leaving 18 patients in the final analysis. The selection process and reasons for exclusion are detailed in Figure 1.

The 18 analyzed patients received a mean of 23.3 ± 0.67 rTMS sessions (range, 22–24) during the 28-day analysis period. Temporary missed sessions occurred for medical reasons, including fever. No patient permanently discontinued rTMS during this period, and no serious adverse events attributed to rTMS were documented among the analyzed patients.

MEPs were recorded in eight of the 18 patients (44.4%). In the remaining 10 patients (55.6%), the rMT criterion could not be met within the tested intensity range of up to 60% MSO, and rTMS was delivered at a fixed intensity of 54% MSO.

Participant characteristics and upper-limb Brunnstrom recovery stages at rTMS initiation are summarized in Table 1.

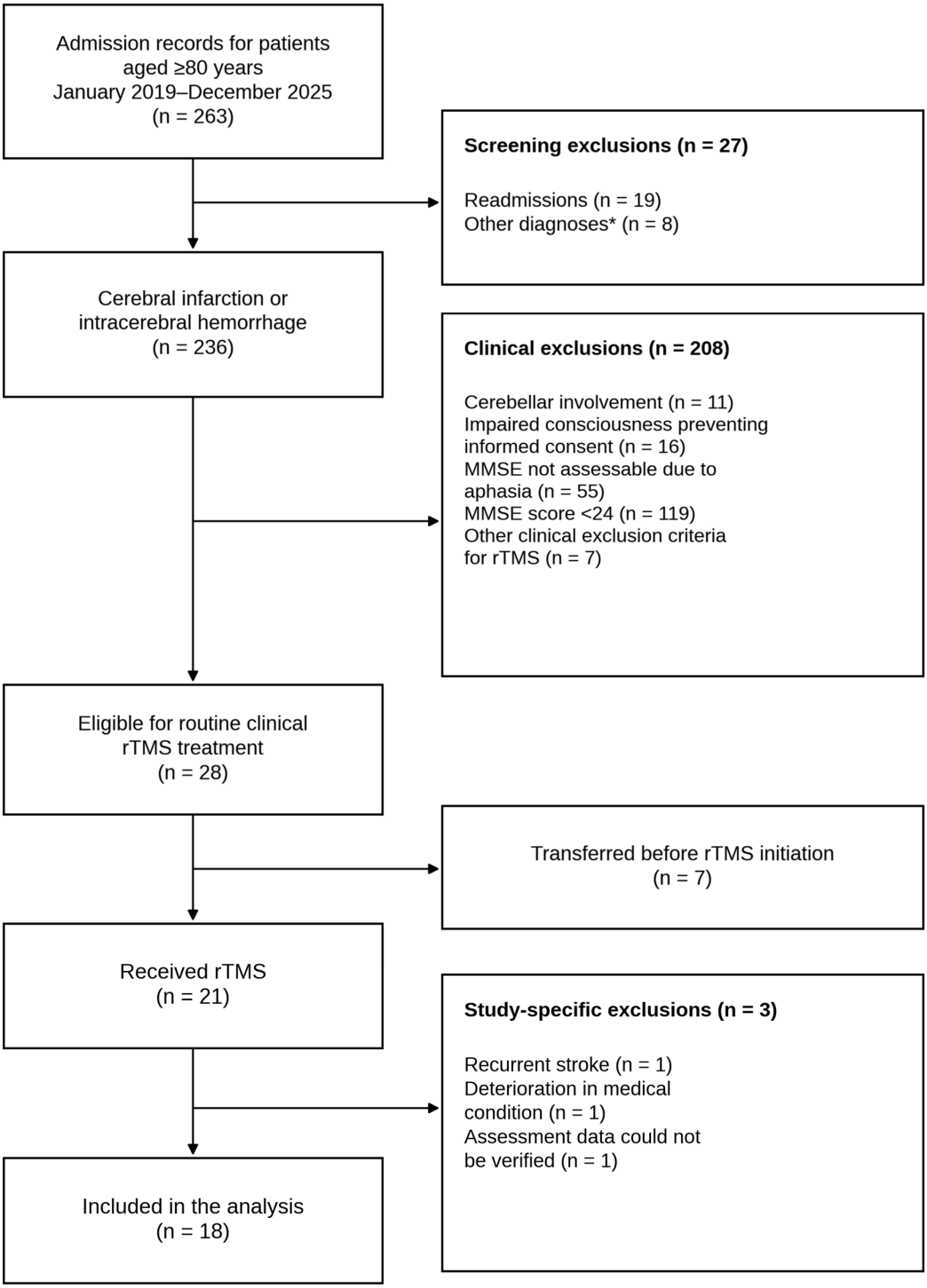

Figure 1. Patient selection from the hospital database between January 2019 and December 2025. The flowchart distinguishes selection for rTMS in routine clinical practice, transfer before treatment initiation, and study-specific exclusions. MMSE, Mini-Mental State Examination; rTMS, repetitive transcranial magnetic stimulation. * Diagnoses other than cerebral infarction or intracerebral hemorrhage.

Table 1. Characteristics of the participants.

Characteristic	Participants ($n = 18$)
Age, years	84.2 ± 3.7
Sex (male/female), *n*	6/12

Table 1. *Cont.*

Characteristic	Participants (n = 18)
Stroke type (ischemic/hemorrhagic), *n*	13/5
Side of paresis (right/left), *n*	8/10
Time from stroke onset to rTMS initiation, days	46.5 ± 12.4
Time from hospital admission to rTMS initiation, days	23.7 ± 11.7
Upper-limb BRS at rTMS initiation (II/III/IV/V), *n*	3/4/7/4

Values are presented as mean ± standard deviation or number of participants. Counts separated by slashes follow the category order shown. BRS, Brunnstrom recovery stage; rTMS, repetitive transcranial magnetic stimulation.

3.2. Upper-Limb Motor Impairment

Mean ± standard deviation FMA-UE scores were 26.83 ± 18.65 at admission, 31.39 ± 16.59 at rTMS initiation, 40.28 ± 17.33 at 2 weeks, and 44.83 ± 17.29 at 4 weeks. In the linear mixed-effects model with assessment time point as a fixed effect and a participant-specific random intercept, the FMA-UE score at 4 weeks was higher than that at rTMS initiation, with an estimated mean difference of 13.44 points (95% CI, 10.35–16.54; Holm-adjusted $p < 0.001$).

FMA-UE scores also increased between admission and rTMS initiation (estimated mean difference, 4.56 points; pointwise 95% CI, 1.46–7.65; Holm-adjusted $p = 0.0093$). Scores increased in 13 patients and were unchanged in 5. All six model-based time-point comparisons are reported in Table 2.

Table 2. Pairwise comparisons of FMA-UE scores across assessment time points.

Comparison (Later Minus Earlier)	Mean Difference (Points)	95% CI (Points)	Holm-Adjusted *p* Value
rTMS initiation minus admission	4.56	1.46–7.65	0.0093
Week 2 minus admission	13.44	10.35–16.54	<0.001
Week 4 minus admission	18.00	14.91–21.09	<0.001
Week 2 minus rTMS initiation	8.89	5.80–11.98	<0.001
Week 4 minus rTMS initiation	13.44	10.35–16.54	<0.001
Week 4 minus week 2	4.56	1.46–7.65	0.0093

Contrasts were estimated from the categorical-time-point linear mixed-effects model with participant-specific random intercepts (18 participants; 72 observations), fitted using restricted maximum likelihood with Kenward–Roger inference. *p* values were adjusted using Holm's method across all six comparisons. The primary contrast was week 4 minus rTMS initiation; the other contrasts were exploratory. CIs are pointwise 95% intervals without multiplicity adjustment. FMA-UE, Fugl-Meyer Assessment of the Upper Extremity; rTMS, repetitive transcranial magnetic stimulation; CI, confidence interval.

FMA-UE scores increased in all 18 patients between rTMS initiation and 4 weeks. The median within-patient change was 12.00 points (first–third quartiles, 9.50–16.00), with a range of 4–31 points. Between rTMS initiation and 4 weeks, FMA-UE increases of at least 9 points and at least 10 points were observed in 14 (77.8%) and 13 (72.2%) of the 18 patients, respectively. The supplementary exact two-sided Wilcoxon signed-rank test supported the direction of the primary result (unadjusted $p < 0.001$; effect size r = 0.879). Individual trajectories and observed mean scores are shown in Figure 2.

3.3. Exploratory Analysis of Recovery Rates

In the exploratory continuous piecewise linear mixed-effects model, the estimated rate of increase in FMA-UE score was 0.227 points/day (95% CI, 0.122–0.333) before rTMS initiation and 0.478 points/day (95% CI, 0.375–0.581) after initiation. The estimated difference in rates (after minus before initiation) was 0.251 points/day (95% CI, 0.072–0.430; unadjusted

$p = 0.007$), indicating a higher estimated rate of improvement after initiation. The p value was not adjusted for multiple comparisons. These estimates are summarized in Table 3.

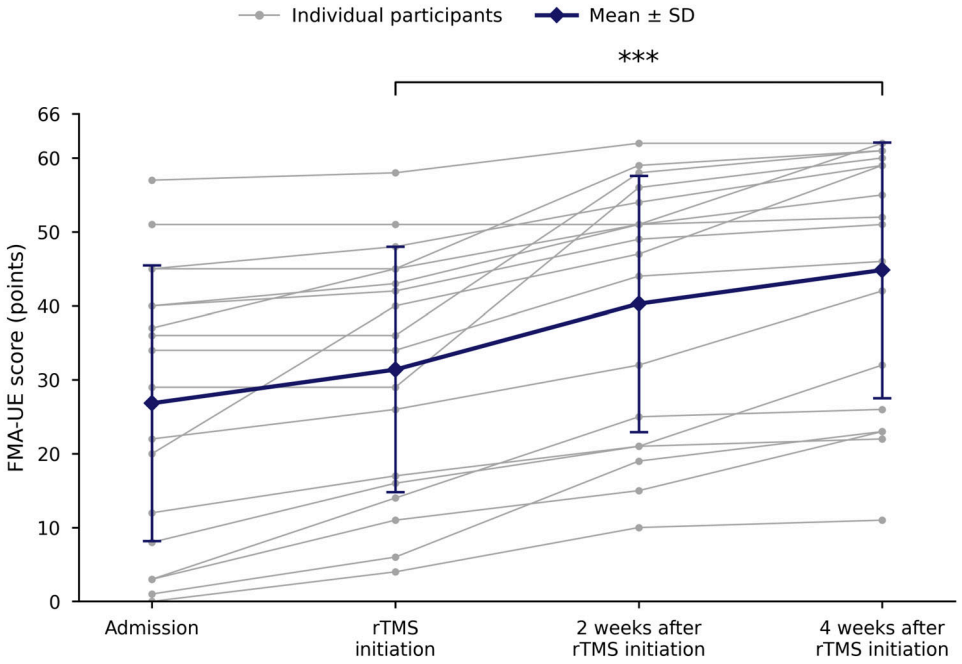

Figure 2. Upper-limb motor impairment across four assessment time points. Gray points and lines show individual FMA-UE scores. Blue diamonds and lines indicate observed means, and error bars indicate standard deviations (SD). All 18 participants had data at all four time points. Admission, rTMS initiation, week 2, and week 4 are displayed as equally spaced assessment categories; their spacing does not represent equal elapsed time. The admission-to-initiation interval varied between participants. The bracket shows only the primary comparison between rTMS initiation and 4 weeks after initiation. p values were obtained from a linear mixed-effects model with categorical assessment time point and participant-specific random intercepts, fitted using restricted maximum likelihood with Kenward-Roger inference, and adjusted using Holm's method across all six pairwise time-point comparisons. *** Holm-adjusted $p < 0.001$. All six comparisons, including the exploratory comparisons, are reported in Table 2. Error bars show observed SD, not model-based confidence intervals. FMA-UE, Fugl-Meyer Assessment of the Upper Extremity; rTMS, repetitive transcranial magnetic stimulation.

Table 3. Estimated rates of change in FMA-UE scores before and after rTMS initiation.

Period or Contrast	Estimate (Points/Day)	95% CI (Points/Day)	Unadjusted p
Before rTMS initiation	0.227	0.122–0.333	—
After rTMS initiation	0.478	0.375–0.581	—
Difference (after minus before)	0.251	0.072–0.430	0.007

Data from 18 participants (72 observations) were analyzed using a continuous piecewise linear mixed-effects model with a knot at rTMS initiation and a participant-specific random intercept. Estimates were obtained by restricted maximum likelihood; 95% confidence intervals and the two-sided p value were calculated using the Kenward–Roger method. Time was expressed in days relative to rTMS initiation (day 0). Admission used each participant's actual interval before initiation; the 2-week and 4-week assessments were represented by days 14 and 28, respectively. The model was constrained to be continuous at initiation. Positive rates indicate increasing FMA-UE scores. The difference is the rate after initiation minus the rate before initiation. The p value tests this difference and was not adjusted for multiple comparisons; the analysis is exploratory. Dashes indicate that tests of individual slopes against zero are not reported. FMA-UE, Fugl-Meyer Assessment of the Upper Extremity; rTMS, repetitive transcranial magnetic stimulation; CI, confidence interval.

3.4. Secondary Outcomes

FIM-motor, WMFT-FAS, and WMFT-Time data were available at rTMS initiation and 4 weeks for all 18 patients, with no missing values. Values below are presented as medians (first–third quartiles). All three comparisons remained significant after Holm adjustment across the secondary outcomes (adjusted $p < 0.001$ for each).

FIM-motor scores increased from 41.50 (31.75–61.50) at rTMS initiation to 57.50 (42.25–76.00) at 4 weeks (exact two-sided Wilcoxon signed-rank test, Holm-adjusted $p < 0.001$; r = 0.879). The median within-patient change was 8.00 (6.25–10.00) points, and scores increased in all 18 patients.

WMFT-FAS scores increased from 3.10 (1.07–4.00) at rTMS initiation to 3.77 (2.80–4.25) at 4 weeks (Holm-adjusted $p < 0.001$; r = 0.879). The median within-patient change was 0.47 (0.20–0.80) points, and scores increased in all 18 patients.

WMFT-Time was 12.00 (6.15–80.66) s at rTMS initiation and 4.36 (3.62–18.12) s at 4 weeks. The median within-patient change (week 4 minus initiation) was −3.33 (−8.74 to −0.58) s. The exact two-sided Wilcoxon signed-rank test performed on natural log-transformed WMFT-Time showed a significant decrease (Holm-adjusted $p < 0.001$; r = 0.816). Completion times decreased in 17 patients and increased in 1, with no unchanged values. Individual changes in the secondary outcomes are shown in Figure 3.

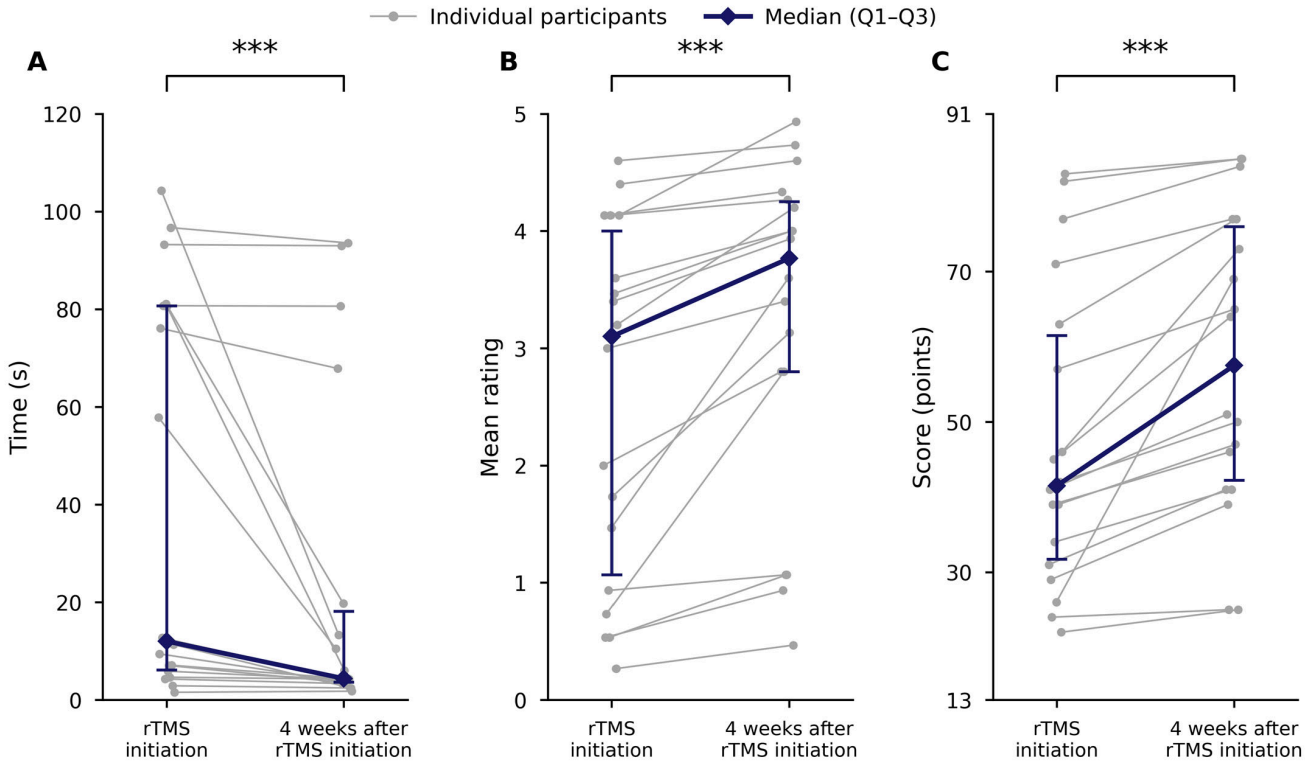

Figure 3. Changes in upper-limb task performance and independence in daily activities. (**A**), WMFT-Time; (**B**), WMFT-FAS; and (**C**), FIM-motor at rTMS initiation and week 4. Gray points and lines connect each participant's measurements ($n = 18$); small horizontal offsets reduce overlap. Blue diamonds and lines show medians; error bars indicate the first and third quartiles. WMFT-Time is the mean completion time across 15 tasks, displayed in seconds on a linear axis; testing used natural log-transformed mean times. Brackets indicate exact two-sided Wilcoxon signed-rank comparisons, with Holm adjustment across the three secondary outcomes; *** adjusted $p < 0.001$. These analyses are exploratory. Shorter times and higher WMFT-FAS and FIM-motor scores indicate better performance. WMFT, Wolf Motor Function Test; FAS, Functional Ability Scale; FIM, Functional Independence Measure; FIM-motor, motor subscale of the Functional Independence Measure; rTMS, repetitive transcranial magnetic stimulation.

4. Discussion

In this retrospective cohort of 18 patients aged 80 years or older with subacute stroke, FMA-UE scores increased by an estimated 13.44 points over 4 weeks after rTMS initiation. Improvements in WMFT-Time, WMFT-FAS, and FIM-motor were also observed. These findings document functional changes during a period in which patients received high-frequency rTMS and rehabilitation. However, spontaneous recovery and concurrent rehabilitation could fully account for these changes; the present study cannot establish an additional contribution of rTMS. Similarly, the higher improvement rate estimated after rTMS initiation in the exploratory piecewise analysis does not establish a treatment effect.

Previous clinical studies and meta-analyses have investigated rTMS combined with rehabilitation for upper-limb motor impairment after stroke [35,36]. In Japan, this approach has been investigated in stroke populations spanning a broad age range. A large multicenter study of low-frequency rTMS combined with intensive occupational therapy allowed enrollment of patients aged up to 90 years but did not report outcomes specifically for those aged 80 years or older [37]. By focusing exclusively on patients aged 80 years or older with subacute stroke, the present study complements this literature with a detailed assessment of upper-limb function and ADL over 4 weeks of high-frequency rTMS combined with rehabilitation. These observations provide descriptive data for an age group that has received limited attention in previous research.

Li et al. [20] reported greater improvements in FMA-UE and Barthel Index scores with 10 Hz rTMS than with sham stimulation. The mean age of the 10 Hz group was 64.2 years, compared with 84.2 years in our cohort. Our patients showed changes in the same direction, although differences in study design and patient characteristics limit direct comparison. Age-related reductions in motor cortical plasticity have been reported in healthy adults using paired associative stimulation [14]. Our study adds descriptive data for patients aged 80 years or older, but does not establish whether age modifies the response to rTMS.

The association between age and recovery is not uniform across studies. Although pooled estimates in the review by Coupar et al. favored younger patients, the evidence for age was considered inconclusive because results differed between analytical approaches [11]. Older age has been associated with smaller early gains in hand function [38]. In an exploratory study of 12 patients with chronic stroke, older age was associated with smaller gains in grip strength after a single session of high-frequency rTMS [39]. Other studies have not consistently identified effects of age or time since stroke on treatment outcomes [10], and improvements in motor function and ADL following routine rehabilitation have also been reported in patients aged 80 years or older [40]. In the present study, FMA-UE scores increased in all 18 patients during combined treatment, although the contribution of rTMS remains unclear.

Neuroplasticity is thought to contribute to functional recovery after stroke [7,41]. Previous research has linked rTMS to synaptic plasticity [35,42], changes in synaptic structure in experimental models of ischemic stroke [43], and changes in serum brain-derived neurotrophic factor (BDNF) levels in patients with stroke [44].

Du et al. [45] reported increased ipsilesional motor cortical excitability following 10 Hz rTMS in patients with early stroke. Facilitating ipsilesional M1 is consistent with the interhemispheric inhibition model, which proposes that excessive contralesional inhibition may impair motor recovery [46]. However, the model may not apply equally to all patients [47]. The functional changes observed here are compatible with this rationale, but do not establish changes in cortical excitability or interhemispheric inhibition.

Aging may reduce motor learning-dependent plasticity and experience-dependent synaptic remodeling [16,48], as well as some plastic responses to noninvasive brain stimulation [14,15]. Nevertheless, evidence from aged stroke models suggests that neural repair

capacity persists. Axonal sprouting has been identified in the peri-infarct cortex of aged animals [49], and chondroitinase ABC treatment has promoted corticospinal sprouting and sensorimotor recovery in aged rats [50]. Stroke-induced neurogenesis also remains partly preserved, particularly in the striatum [51]. Experimental studies have linked rTMS to neurotrophic signaling and modulation of inflammatory responses [43], while clinical literature describes BDNF-related changes during rTMS combined with rehabilitation [52]. These findings from previous studies provide a rationale for further investigation of rTMS and rehabilitation in older patients, but the present study did not assess neuroplasticity.

Limitations and Future Directions

Several limitations should be considered. First, this was a retrospective, single-center observational study with a small sample of 18 patients. The high exclusion rate reflects our institutional clinical selection criteria, including an MMSE score below 24 and inability to complete the MMSE because of aphasia. At our institution, the clinical eligibility rate for rTMS was 11.9% among patients aged 80 years or older and 14.0% among patients aged 18–79 years. Our findings therefore apply to selected patients aged 80 years or older who met these criteria and could complete follow-up assessments, and may not be generalizable to patients excluded under this protocol. Second, there was no sham-stimulation or rehabilitation-only control group. The contributions of high-frequency rTMS, concurrent rehabilitation, and spontaneous recovery therefore cannot be separated. Third, the analysis was limited to the first 4 weeks of combined treatment. Longer treatment periods may yield different patterns of functional change, and longer follow-up is needed to determine whether the observed improvements are sustained. Fourth, FIM-motor is influenced by factors other than upper-limb function, so improvements in ADL cannot be attributed solely to upper-limb recovery.

Outcome assessments, including the FMA-UE, were performed as part of routine clinical care by assessors who were not blinded to treatment. This may have introduced measurement (detection) bias and influenced the observed changes.

MEP elicitability is an important prognostic factor after stroke [13]. In this cohort, MEPs were recorded in eight patients, whereas the rMT criterion could not be met within the tested intensity range in 10 patients. Because intensities above 60% MSO were not tested, these 10 patients cannot be classified as definitively MEP-negative. Differences in corticospinal function may have contributed to variation in the observed outcomes. In addition, fixed stimulation at 54% MSO cannot be assumed to be physiologically equivalent to stimulation at 90% of an individually determined rMT. The small sample did not permit reliable subgroup comparisons, and the findings do not establish comparable outcomes between these subgroups.

In addition, the exploratory piecewise model estimated the rate of FMA-UE improvement before rTMS initiation from only two assessments per patient, at admission and rTMS initiation. Post-initiation assessments were treated as occurring on days 14 and 28 after rTMS initiation. The estimated difference in slopes should therefore be interpreted cautiously.

Larger multicenter studies and prospective randomized trials with sham stimulation are needed to evaluate the efficacy and safety of this intervention in patients aged 80 years or older. Future studies should also examine whether neurophysiological measures, including MEP presence, amplitude, and latency, can predict treatment response. The potential roles of lesion location and corticospinal tract integrity in guiding individualized rTMS protocols warrant further investigation.

5. Conclusions

In this selected cohort of patients aged 80 years or older with subacute stroke, upper-limb function and ADL measures improved over 4 weeks during which patients received high-frequency rTMS and rehabilitation. No serious adverse events attributed to rTMS were documented among the analyzed patients. These observations do not establish an additional benefit of rTMS beyond spontaneous recovery and rehabilitation. Prospective controlled studies are needed to determine whether adding rTMS to rehabilitation improves outcomes in this population.

Author Contributions: Conceptualization, R.N. and M.N.; methodology, R.N., M.N. and T.Y.; formal analysis, R.N.; investigation, R.N., M.F., W.N., T.F., R.T., R.K., Y.M., Y.O., C.F. and T.Y.; data curation, R.N. and M.F.; writing—original draft preparation, R.N.; writing—review and editing, R.N., M.N., M.F., W.N., T.F., C.F. and T.Y.; visualization, R.N.; supervision, M.N. and T.Y.; project administration, M.N. and T.Y.; funding acquisition, M.N. All authors have read and agreed to the published version of the manuscript.

Funding: This work was partially supported by JSPS KAKENHI (Grant Number 24K20542) to M.N.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Sonodakai Institutional Review Board (approval No. 225; approval date: 29 September 2026).

Informed Consent Statement: An opt-out procedure was used for this retrospective study. Study information was posted within the hospital, and patients were given the opportunity to decline participation. Written and verbal consent for rTMS treatment was obtained separately.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: We thank the patients who contributed to this study, the staff of the Department of Rehabilitation at Sonodakai Neurorehabilitation Hospital, and our mentors for their guidance. During the preparation of this manuscript, the authors used ChatGPT (version: GPT-6 Astra; OpenAI, San Francisco, CA, USA) for English translation, language editing, and assistance with code generation for statistical analysis and figure preparation. The authors reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ADL	Activities of daily living
APB	Abductor pollicis brevis
BDNF	Brain-derived neurotrophic factor
BRS	Brunnstrom recovery stage
CI	Confidence interval
FAS	Functional Ability Scale
FIM	Functional Independence Measure
FIM-motor	Motor subscale of the Functional Independence Measure
FMA-UE	Fugl-Meyer Assessment of the Upper Extremity
M1	Primary motor cortex
MCID	Minimal clinically important difference
MEP	Motor evoked potential
MMSE	Mini-Mental State Examination
MSO	Maximum stimulator output
PREP2	Predict Recovery Potential 2
rMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation

SAFE	Shoulder Abduction and Finger Extension
SD	Standard deviation
TMS	Transcranial magnetic stimulation
WMFT	Wolf Motor Function Test
WMFT-FAS	Wolf Motor Function Test Functional Ability Scale
WMFT-Time	Wolf Motor Function Test time

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