

From trials to practice: contralesional 1 Hz rTMS in chronic stroke - a first real-world retrospective cohort of 112 patients treated in routine outpatient care

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Research Article

Keywords: repetitive transcranial magnetic stimulation, chronic stroke, spasticity, upper limb, real-world data, neurorehabilitation

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10941155/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background.

Low-frequency contralesional repetitive transcranial magnetic stimulation (rTMS) carries a guideline recommendation for post-stroke motor rehabilitation, but the evidence derives largely from controlled trials in selected post-acute to subacute cohorts, and the largest chronic-stroke trial showed no benefit on its primary motor outcome. Real-world data on chronic stroke under routine outpatient conditions are scarce.

Methods.

We retrospectively analyzed 112 patients with chronic stroke (mean age 61 years; median 3 years post-stroke) who completed a routine outpatient treatment program between 2019 and 2025 comprising neuronavigated 1 Hz rTMS over the contralesional primary motor cortex (1,200 pulses at 120% of resting motor threshold per session) plus conventional therapy over either 3 or 6 weeks. Outcomes were the upper-extremity Fugl-Meyer Assessment (FMA-UE), Modified Ashworth Scale (mAS) at six joints, relative grip strength, and contralesional resting motor threshold (RMT), assessed 1–3 days before the first and 0–3 days after the final rTMS session, and analyzed with paired tests, ANCOVA, and multivariable linear regression.

Results.

Spasticity scores decreased at every joint (all Bonferroni-corrected $p \leq 0.002$; effect size 0.34–0.51), largest proximally. FMA-UE increased by 3.94 points (95% CI 3.02–4.85; $d = 0.80$); 74% improved and 43% reached the ≥ 5 -point MCID. ANCOVA showed a positive association between baseline FMA-UE and subsequent FMA-UE change (slope 1.09, 95% CI 1.03–1.16), and change differed across baseline severity tertiles ($p = 0.005$). A multivariable model of Δ FMA-UE on baseline FMA-UE, age, time since stroke, sex, stroke type, care pathway, and affected hemisphere was not significant, and its coefficients are exploratory only. Grip strength did not change. Contralesional RMT increased slightly ($d = 0.27$) but did not track clinical change. Time since stroke was not associated with change in FMA-UE or mAS-derived scores.

Conclusions.

In this real-world chronic-stroke cohort, reduction in modified Ashworth-derived scores was the most directionally consistent pre-post change across the assessed clinical domains, whereas motor gains were smaller and positively associated with baseline FMA-UE scores. These uncontrolled findings support prospective evaluation of spasticity-related outcomes in controlled trials. They do not support using time since stroke as an exclusion criterion in this treatment pathway.

Trial registration:

not registered.

Background

Stroke is a leading cause of long-term disability (1), and upper-limb motor impairment is among its most persistent consequences (2). Repetitive transcranial magnetic stimulation (rTMS) has been studied as an adjunct to rehabilitation for more than two decades. The evidence base is large but heterogeneous, with meta-analyses reporting small-to-moderate gains in motor impairment alongside substantial between-study variability, while high-powered single trials have repeatedly failed to confirm benefit over sham (3–6). Sources of this variability are well documented and include differences in stimulation protocol, targeted hemisphere, dose, outcome selection, and heterogeneity of the stroke population itself (7–9). Recent broad syntheses underline both the maturation of the field and the persistent gap between controlled-trial evidence and routine clinical implementation (10).

For contralesional low-frequency rTMS in particular, the mechanistic rationale is grounded in the interhemispheric inhibition model of Murase and colleagues (11), in which unilateral motor cortex (M1) damage releases the contralesional hemisphere from reciprocal inhibition and the resulting transcallosal drive then constrains output from the ipsilesional M1. Excitability-depressing low-frequency rTMS over the contralesional M1 was conceived to reduce this maladaptive inhibition and re-open the ipsilesional hemisphere to plasticity (12–14). This protocol carries a Level A recommendation in the 2020 European guidelines for the post-acute stage of upper-limb motor stroke and a Level C recommendation for the chronic stage (15).

The dominant outcome measure of the existing evidence base has been voluntary motor performance, typically the upper-extremity Fugl-Meyer Assessment (FMA-UE) (3, 16–19), with spasticity treated as a secondary or omitted measure even though it affects an estimated 97% of stroke patients with moderate-to-severe motor deficit and is a primary driver of disability and caregiver burden (20–24). Furthermore, the majority of trials enrolled patients within the first weeks to months after stroke, on the prevailing assumption that windows of neuroplasticity narrow over time, a view recently reinforced by the CPASS Phase II trial, which identified a sensitive period for motor training in the first months after stroke (25–27). As a consequence, the chronic stage has been comparatively understudied, and rTMS in chronic stroke is widely regarded as, at best, a marginal intervention.

However, both features deserve to be questioned. A growing line of work suggests that spasticity responds to non-invasive brain stimulation through supraspinal tone-regulating pathways that need not co-vary with corticospinal motor recovery (28–30) and that the chronic stage retains plastic capacity in domains other than fine voluntary motor control (31–33). If correct, then current evidence may be underestimating treatment effects either by measuring the wrong outcome or by measuring the right outcome in the wrong patients.

What is largely missing from this literature is real-world data. Most published cohorts are small, controlled, and selected for protocol fit; it is therefore unclear how far the findings extend to chronic stroke patients under routine outpatient conditions. Such data cannot replace controlled trials. They address a different question, namely which clinical domains change, by how much, and in whom, among the patients who actually present for rTMS at this stage.

The TMS outpatient clinic at the Department of Neurology and Stroke at the University Hospital Tübingen, established in 2019, was among the first centers in Europe to implement an rTMS program as a structured outpatient service for chronic post-stroke motor deficit. Over seven years, 112 patients have completed the

program with standardized pre- and post-intervention assessment. We analyzed this cohort to determine which changes were observed across motor impairment, spasticity, grip strength, and contralesional corticospinal excitability, and whether these observations vary with time since stroke or with baseline patient characteristics. For the clinical measures the expectation was improvement. For contralesional corticospinal excitability, the mechanistic rationale of the protocol predicts reduced excitability of the stimulated hemisphere, that is, an increase in contralesional resting motor threshold; we therefore also asked whether such a change occurred and whether its magnitude tracked clinical change at the individual level, as would be required for it to serve as a marker of response. Given the design, the analysis is descriptive and hypothesis-generating, and explicitly not a test of efficacy.

Methods

Study design and setting

This is a retrospective analysis of 112 patients treated in the rTMS outpatient clinic at the Department of Neurology and Stroke, University Hospital Tübingen, between January 2019 and December 2025. The clinic provides structured contralesional 1 Hz rTMS programs for adults with chronic post-stroke deficits, covering both upper-limb motor impairment and non-fluent (motor) aphasia. The present analysis is restricted to the upper-limb motor protocol; outcomes of the aphasia protocol will be reported separately. Patients predominantly self-referred to the clinic, with a smaller proportion referred from inpatient and outpatient neurorehabilitation services or by community-based physicians. Patients traveled to the clinic from across Germany and from neighboring countries. Patients were assessed before and after the rTMS course according to a standing clinical protocol, established in 2019, which specified eligibility criteria, stimulation parameters, and the assessment battery.

This retrospective analysis was approved by the Ethics Committee of the Medical Faculty of Eberhard Karls University Tübingen and the University Hospital Tübingen (reference 2026 – 0203) and was conducted in accordance with the Declaration of Helsinki. Written informed consent for treatment and use of clinical data for retrospective research was obtained from each patient. Study-specific informed consent was waived under the approved protocol.

Participants

During the observation period, 120 patients commenced the contralesional 1 Hz rTMS program and are reported here. All patients who received this protocol were included consecutively; no selection was applied within this group. Patients treated during the initial months after the service was established, when stimulation parameters still varied and before the protocol was standardized to the parameters that now carry a guideline recommendation, were not included in the present analysis. Eight of the consecutive 120 were not included in the analysis: four discontinued the planned stimulation course for reasons unrelated to rTMS (three discontinuations related to the COVID-19 pandemic and one road traffic accident; none were stimulation-related adverse events), and four received an extended treatment course without a completed post-intervention assessment. The analyzed cohort comprises the 112 patients who completed the program during the observation period and contributed matched pre- and post-treatment assessments. Because no systematic log

of referred but non-enrolled patients was maintained, the analysis does not permit quantification of selection before program initiation. The clinical records indicated that non-enrollment occurred in a small number of individual cases because of failure to meet the diagnostic inclusion criteria (e.g., motor deficits attributable to brain tumor or Parkinson's disease), predominantly subjective deficits without an objectively treatable motor impairment, or presence of TMS contraindications (e.g., a ventriculoperitoneal shunt). The present figures therefore describe the post-enrollment flow only (Fig. 1).

Inclusion in the clinic followed the criteria of the standing clinical protocol, comprising ischemic or hemorrhagic stroke confirmed by neuroimaging, a persisting and clinically objectifiable upper-limb motor deficit, at least 3 months elapsed since stroke onset, no contraindications to TMS (34), and stable rehabilitation status defined as no change in spasticity-modifying medication and no botulinum toxin injection within the preceding three months. There were no a priori cutoffs for baseline FMA-UE or baseline mAS.

Time since stroke was recorded in completed years and ranged from less than one year (recorded as 0) to 21 years (median 3, IQR 1–6). Eight patients had an interval between 3 and 12 months between stroke and rTMS. The cohort therefore covers the late-subacute to long-chronic range, with the majority of patients beyond one year post-stroke.

Intervention

All patients received 1 Hz rTMS over the contralesional M1. In each session 1,200 pulses were delivered at 120% of the resting motor threshold (RMT) of the contralesional M1. Stimulation was delivered according to the 2020 European guidelines (15). Safety procedures followed Rossi et al. 2021 (34). Until December 2021, stimulation was delivered with a Nexstim NBT System 2 with integrated MRI-based neuronavigation (Nexstim Plc, Helsinki, Finland; n = 27). From January 2022 onward, stimulation was delivered with a Magstim Horizon system and a 70-mm air-cooled figure-of-eight coil (Magstim Company Ltd., Whitland, UK), with coil position tracked online using a Localite TMS-Navigator system (Localite GmbH, St. Augustin, Germany; n = 85). In both configurations, neuronavigation was co-registered to each patient's individual T1-weighted MRI and coil displacement during a session was kept within 2 mm.

Treatment was embedded in one of two care pathways, which determined both the rTMS schedule and the adjunctive therapy. Patients enrolled in the multimodal outpatient neurorehabilitation program at the cooperating Center for Outpatient Rehabilitation (ZAR) Tübingen (n = 57) received 15 rTMS sessions over three weeks (five sessions per week), each followed immediately by a 50-minute session of occupational therapy. The rTMS-occupational therapy combination was embedded in the outpatient neurorehabilitation program, which additionally included physiotherapy, sports and physical therapy, speech and language therapy, neuropsychological treatment, and social counseling as clinically indicated. Patients in the standard statutory outpatient physiotherapy pathway ("Heilmittelverordnung") received 18 rTMS sessions over six weeks (three sessions per week), each followed by a 50-minute physiotherapy session at the University Center for Physiotherapy under the prescription (n = 55). The two schedules delivered broadly comparable, but not identical, cumulative stimulation doses (18,000 versus 21,600 pulses) and differed in treatment duration and the amount of concurrent rehabilitation delivered. In both pathways, the adjunctive therapy began within approximately 15 minutes of each rTMS session in order to exploit the stimulation-induced window of cortical

plasticity, focused on the paretic upper limb, and was individually tailored to the patient at the treating therapist's discretion. Schedule assignment was driven by referral source, insurance reimbursement structure, and logistical feasibility for the patient, not systematically by clinical phenotype.

Outcomes

All assessments were performed at two time points, baseline (1–3 days before the first rTMS session) and post-intervention (0–3 days after the final session).

Motor impairment. The upper-extremity Fugl-Meyer Assessment (FMA-UE), a 66-point scale (16, 17), was the primary motor-impairment measure, with subscores recorded for upper extremity (maximum 36 points), wrist (maximum 10 points), hand (maximum 14 points), and coordination/speed (maximum 6 points).

Spasticity. The Modified Ashworth Scale (mAS) (35, 36) was rated at six joint segments of the affected upper limb, namely shoulder, elbow, forearm (pronation), wrist, fingers, and thumb. To improve granularity, each joint was examined in multiple movement directions, four directions at the shoulder (flexion/extension and abduction/adduction with internal/external rotation) and two opposing directions at each of the other five joints (flexion/extension, or pronation/supination at the forearm). Each per-direction rating used the standard six-step Modified Ashworth Scale (grades 0, 1, 1+, 2, 3, 4), which we converted to a numeric scale (grade 1 + recoded as 2 and the subsequent grades renumbered accordingly, so that the original grade 4, "affected part rigid in flexion or extension", corresponds to a numeric value of 5), an operationalization that addresses the ordinal ambiguity between the "1" and "1+" grades documented by Pandyan et al. (37). For analysis, the per-joint mAS was computed as the arithmetic mean of the per-direction ratings at that joint. The resulting per-joint scores therefore range from 0 to 5 in 0.5-point steps for the five two-direction joints, and from 0 to 5 in 0.25-point steps for the shoulder, where four ratings were averaged. Lower scores indicate less spasticity; for clarity in the Results, change scores are reported with the convention that a negative pre-post change reflects improvement.

Grip strength. Grip strength of the paretic hand was measured with a vigorimeter and expressed as a percentage of the unaffected hand (38). This measure was introduced into the routine clinical protocol in 2023 and was therefore available for 53 patients with matched pre- and post-intervention measurements.

Corticospinal excitability. The RMT of the contralesional M1 was determined at both time points by visual inspection of the contralateral first dorsal interosseous muscle, defined as the minimum stimulator intensity (as a percentage of maximum stimulator output) required to evoke a visible muscle twitch in at least 5 of 10 consecutive single-pulse trials with the muscle at rest. Surface electromyography (EMG) was not available in the outpatient clinical setting, so the EMG-based criterion of motor evoked potentials exceeding 50 μ V recommended by current guidelines of the International Federation of Clinical Neurophysiology could not be applied (39). Visual determination has been reported to yield higher threshold estimates than the EMG-based method (40). Contralesional RMT was available in all 112 patients.

Assessors. Clinical and neurophysiological assessments were performed by experienced study personnel of the Department of Neurology and Stroke, predominantly by one senior rater who also led internal rater training. Raters were not exclusively assigned to the rTMS service, and assessment was organized to be separate from rTMS delivery wherever staffing allowed. Assessments were performed blinded to treatment time point

wherever the routine workflow permitted, and the majority of assessments were carried out on this basis. However, full and uniform blinding could not be guaranteed throughout because of staffing constraints.

Statistical analysis

Clinical measures (FMA-UE, mAS, grip strength) were defined as the primary outcome domains; contralesional RMT was treated as a secondary, exploratory outcome. All analyses were conducted in IBM SPSS Statistics version 31. Tests were two-tailed with $\alpha = 0.05$. Confidence intervals for proportions are Wilson score intervals. No a priori sample-size calculation was performed.

Pre-post change. Pre-post change in FMA-UE was tested with a paired t-test. Distributional checks (Shapiro-Wilk $W = 0.96$ for Δ FMA-UE, $p = 0.003$; visual inspection of histograms and Q-Q plots) showed mild departures from normality; given $n = 112$, the paired t-test is robust to this, and Wilcoxon signed-rank served as a sensitivity test. Effect sizes are reported as Cohen's d for paired samples with 95% confidence intervals. Pre-post change in each of the six mAS joint segments was tested with Wilcoxon signed-rank as the primary test (chosen a priori because the per-joint mAS averages aggregate ordinal per-direction ratings and are therefore not formally interval-scaled); paired t-tests are reported alongside for comparability with prior literature. For Wilcoxon tests, effect sizes are reported as $r = Z / \sqrt{N}$ (Rosenthal). Bonferroni correction was applied across the six mAS segments (adjusted $\alpha = 0.0083$); both raw and corrected p-values are reported. Pre-post changes in grip strength and RMT were tested with paired t-tests and confirmed with Wilcoxon.

Baseline-conditional change in motor impairment. The standard approach of correlating baseline FMA-UE with raw change is inferentially complicated by regression to the mean. We therefore complemented the descriptive Spearman correlation between baseline FMA-UE and Δ FMA-UE with an ANCOVA-style linear model regressing post-intervention FMA-UE on baseline FMA-UE. The slope of this model is directly interpretable, in that a slope below 1 indicates regression to the mean, a slope of exactly 1 indicates that the average pre-post difference is independent of baseline, and a slope greater than 1 indicates that higher-baseline patients improve disproportionately more, a pattern that cannot be produced by regression to the mean alone. The same ANCOVA approach was applied to each mAS joint segment as a sensitivity check for baseline-conditional spasticity change.

Predictors of motor change. To identify clinical predictors of Δ FMA-UE, a multivariable linear regression was fitted with baseline FMA-UE, age at treatment, time since stroke (years), sex, stroke type (ischemic vs hemorrhagic), care pathway (outpatient neurorehabilitation program vs standard outpatient prescription), and affected hemisphere (left vs right hemiparesis) as predictors. Tolerance and variance inflation factors were used to check collinearity. The model was prespecified on the variables routinely documented, and no automated variable selection was performed.

Subgroup analyses. Baseline FMA-UE was stratified into three prespecified severity categories corresponding to equal thirds of the 0–66 FMA-UE range (severe 0–22, moderate 23–44, mild 45–66), referred to as severity tertiles throughout. Change across these categories was compared with the Kruskal-Wallis test, followed by pairwise Mann-Whitney post-hoc comparisons with Bonferroni adjustment within this family of three comparisons. No formal interaction terms were fitted, in keeping with the descriptive design.

Care pathway. The two care pathways (outpatient neurorehabilitation program versus standard outpatient prescription) were compared post hoc using the Mann-Whitney U test for continuous and modified Ashworth-derived outcomes, Fisher's exact test for proportions, and independent-samples t-tests for the reported mean differences and their confidence intervals. The comparison was additionally adjusted for baseline FMA-UE, and for baseline FMA-UE together with treatment period, in linear models of post-intervention FMA-UE. This comparison is exploratory and was not prespecified.

Associations across domains. Cross-domain associations (Δ FMA-UE vs Δ mAS by joint, Δ contralesional RMT vs all clinical changes, baseline mAS vs change at the same joint) were assessed with Spearman rank correlation, given the ordinal mAS and the non-normal distribution of several change scores.

Missing data. FMA-UE and contralesional RMT were complete in all 112 patients. One patient had completely missing mAS assessments at both pre- and post-intervention across all six joint segments; analyses of the mAS therefore use the 111 matched pairs available at every joint. Grip strength was available in 53 matched pre/post pairs; the missing-at-design pattern (introduced from 2023 onwards) was not informative of clinical response, but the smaller sample limits power for grip-strength analyses. No imputation was performed.

Multiplicity. Bonferroni correction was applied to the six prespecified mAS segment comparisons. All other analyses (ANCOVA, multivariable regression, severity-tertile post-hoc comparisons, subscore tests, cross-domain Spearman correlations, and the post-hoc comparison by care pathway) were exploratory; apart from the six mAS segment comparisons and the three pairwise tertile comparisons, no further correction for multiplicity was applied. P-values from those analyses are descriptive and not confirmatory.

Reporting. This study is reported in accordance with the STROBE statement for observational studies, and the completed checklist is provided as Additional File 1.

Results

Cohort characteristics

The cohort comprised 112 patients with chronic upper-limb motor deficit after stroke (Table 1). Median time since stroke was 3 years (IQR 1–6, range less than 1 to 21 years); eight patients (7.1%) were treated between 3 and 12 months post-stroke, the protocol-mandated minimum interval, while 104 patients (92.9%) were beyond one year and 5 patients (4.5%) beyond 10 years. At baseline, 68 patients (61%) fell into the severe FMA-UE category (0–22 points), 34 (30%) into the moderate category (23–44 points), and 10 (9%) into the mild category (45–66 points). Occupational therapy at the rehabilitation center and physiotherapy at the University Center for Physiotherapy were balanced across the cohort (57 vs 55 patients). No serious adverse events were recorded. Transient scalp discomfort or mild headache occurred occasionally and did not lead to treatment discontinuation.

Table 1
Baseline characteristics of the analyzed cohort (n = 112).

Characteristic	Value
Age at treatment, years (mean $\pm$ SD; median [IQR]; range)	61.2 $\pm$ 11.7; 61 [56–70]; 27–87
Sex, n (%) - female / male	42 (37.5) / 70 (62.5)
Time since stroke, years (mean $\pm$ SD; median [IQR]; range)	3.8 $\pm$ 3.5; 3 [1–6]; <1 to 21
< 1 year, n (%)	8 (7.1)
1–3 years, n (%)	62 (55.4)
4–10 years, n (%)	37 (33.0)
> 10 years, n (%)	5 (4.5)
Stroke type, n (%) - ischemic / hemorrhagic	75 (67.0) / 37 (33.0)
Affected side, n (%) - left hemiparesis / right hemiparesis	76 (67.9) / 36 (32.1)
Care pathway, n (%) - outpatient neurorehabilitation program (15 sessions, 3 weeks) / standard outpatient prescription “Heilmittelverordnung” (18 sessions, 6 weeks)	57 (50.9) / 55 (49.1)
Baseline FMA-UE total, /66 (mean $\pm$ SD; median [IQR]; range)	21.6 $\pm$ 14.4; 17 [11–32]; 0–62
Severe (0–22), n (%)	68 (60.7)
Moderate (23–44), n (%)	34 (30.4)
Mild (45–66), n (%)	10 (8.9)
Baseline contralesional RMT, % MSO (mean $\pm$ SD)	48.8 $\pm$ 9.3

Values are n (%) unless otherwise indicated. FMA-UE, Fugl-Meyer Assessment Upper Extremity; RMT, resting motor threshold; MSO, maximum stimulator output.

Spasticity score change across joint segments

Modified Ashworth Scale scores decreased after rTMS at all six assessed joint segments (Table 2, Fig. 2). On Wilcoxon signed-rank tests, all changes survived Bonferroni correction for six comparisons (adjusted α = 0.0083; all corrected p < 0.001 except forearm, p = 0.002). Effect sizes ($r = Z / \sqrt{N}$) ranged from 0.34 (forearm) to 0.51 (shoulder), with the largest reductions at proximal joints. At the shoulder, 65 of 111 patients (59%) improved, 19 (17%) worsened, and 27 (24%) showed no change; this pattern was similar in direction across segments though the effect sizes attenuated distally. Among the 19 patients whose shoulder score increased, the median increase was 0.50 points (range 0.25 to 1.75); in seven of them the increase corresponded to a single grade step in one of the four assessed movement directions, which is the smallest change the

composite score can resolve. Median changes ranged from – 0.5 (elbow) to 0 (forearm, wrist, finger, thumb), reflecting the discreteness of the per-joint averages; mean changes were negative across all joints and ranged from – 0.26 (forearm) to – 0.44 (shoulder).

In a post-hoc, descriptive analysis, and to allow comparison with published minimal clinically important difference estimates for the Modified Ashworth Scale (41), a composite of the three muscle groups used in that work was formed for each patient as the mean of the elbow, wrist, and finger scores. This composite decreased from 1.59 ± 1.06 to 1.23 ± 0.95 , a mean change of – 0.37 points (95% CI – 0.48 to – 0.26; Wilcoxon $p < 0.001$), with a standardized response mean of 0.62, that is, the mean change divided by the standard deviation of the change, corresponding to moderate responsiveness on the criteria applied in that work. The values of 0.48 and 0.76 points are the distribution-based minimal clinically important differences reported there for upper-limb muscles, corresponding to effect sizes of 0.5 and 0.8 standard deviations of the baseline scores; the lower threshold is the one recommended for severely impaired patients in whom only a small gain is expected. Forty-four of 111 patients (39.6%; 95% CI 31.0 to 48.9) reached the 0.48-point threshold, and 26 (23.4%; 95% CI 16.5 to 32.1) the 0.76-point threshold.

Table 2
Pre-post change in Modified Ashworth Scale by joint segment (n = 111 at every joint).

Joint	Pre (mean ± SD)	Post (mean ± SD)	Δ (mean ± SD)	Δ 95% CI	Median Δ	Wilcoxon p (raw)	Wilcoxon p (Bonf.)	r	Improved/ Worsened/ Unchanged
Shoulder	1.70 ± 1.18	1.26 ± 1.04	–0.44 ± 0.80	–0.59 to – 0.29	–0.25	< 0.001	< 0.001	0.51	65 / 19 / 27
Elbow	1.84 ± 1.24	1.43 ± 1.20	–0.41 ± 0.79	–0.55 to – 0.26	–0.5	< 0.001	< 0.001	0.45	58 / 17 / 36
Forearm	1.55 ± 1.42	1.30 ± 1.33	–0.26 ± 0.96	–0.44 to – 0.08	0.0	< 0.001	0.002	0.34	43 / 12 / 56
Wrist	1.54 ± 1.37	1.20 ± 1.16	–0.34 ± 0.88	–0.50 to – 0.17	0.0	< 0.001	< 0.001	0.39	44 / 16 / 51
Finger	1.41 ± 1.29	1.05 ± 1.15	–0.36 ± 0.86	–0.53 to – 0.20	0.0	< 0.001	< 0.001	0.38	51 / 16 / 44
Thumb	1.10 ± 1.31	0.76 ± 1.14	–0.34 ± 1.06	–0.54 to – 0.14	0.0	< 0.001	< 0.001	0.36	47 / 11 / 53

Adjusted $\alpha = 0.0083$ for six comparisons. Negative Δ values reflect score reduction (less spasticity). $r = Z / \sqrt{N}$ (Rosenthal effect size for paired Wilcoxon).

The relationship between baseline severity and change at the same joint was consistent, with higher baseline spasticity associated with greater treatment-related reduction at every joint (Spearman ρ between 0.40 and 0.66, all $p < 0.001$). The gradient was steepest at the thumb ($\rho = 0.66$) and comparable across the remaining

joints (p 0.40 to 0.49). An ANCOVA-style check for regression to the mean (post-on-pre slope per joint) returned slopes below 1 in all six segments (range 0.55–0.77; all 95% CI excluded 1), indicating that part of the baseline-change association is consistent with regression to the mean; however, all post-intervention intercepts were small and positive, so net group-level reductions remained after accounting for this baseline-conditional pattern.

Reductions in shoulder, elbow, and wrist spasticity scores were moderately intercorrelated (pairwise p between 0.23 and 0.36, all $p < 0.02$), suggesting that spasticity score change across proximal-to-mid segments tended to move together; finger and thumb reductions clustered with each other ($p = 0.51$, $p < 0.001$) but less so with proximal segments. Reductions in spasticity scores were not significantly associated with time since stroke at any joint (all $|p| < 0.16$, all $p > 0.10$), and the response did not differ between patients treated within the first year post-stroke and those treated later (all per-joint Mann-Whitney $p > 0.20$).

Motor impairment: FMA-UE

FMA-UE increased from 21.6 ± 14.4 at baseline to 25.6 ± 16.4 post-intervention, a mean change of + 3.94 points (95% CI 3.02 to 4.85; $t(111) = 8.44$, $p = 1.4 \times 10^{-13}$; Cohen's $d = 0.80$; Wilcoxon $p = 1.8 \times 10^{-12}$; Table 3, Fig. 3). Eighty-three patients (74.1%; 95% CI 65.3–81.3) showed any improvement, 48 (42.9%; 95% CI 34.1–52.1) reached the ≥ 5 -point threshold for minimal clinically important difference proposed for chronic stroke populations (42), and 18 (16.1%; 95% CI 10.4–24.0) improved by ≥ 10 points. Sixteen patients (14.3%) showed a numerical worsening and 13 (11.6%) were unchanged. In most of these 16 patients the decrease was small, with a median of – 1.5 points (IQR – 3.3 to – 1.0), and 8 of the 16 decreased by a single point. Three patients decreased by 5, 7, and 8 points, that is, by at least the 5-point threshold applied here in the direction of improvement. Expressed relative to baseline motor capacity, 46 of 111 patients (41.4%) improved by up to 25% of their baseline score, 20 (18.0%) by more than 25% up to 50%, and 16 (14.4%) by more than 50% (Table 4). One patient with a baseline FMA-UE of 0 was not included in this relative-change analysis (Table 4), because relative change is undefined at a baseline of zero. All analyses of absolute change, including Table 3 and Fig. 3, are based on all 112 patients. No floor or ceiling effects of analytic concern were observed, since at baseline 3 patients (2.7%) scored ≤ 2 and none scored ≥ 64 , while post-intervention 2 patients scored ≤ 2 and 1 scored ≥ 64 .

Subscore analysis (Table 3) showed that gains were carried by the upper-extremity (proximal arm, $\Delta = +2.21$, $d = 0.69$, $p < 0.001$), wrist ($\Delta = +0.53$, $d = 0.41$, $p < 0.001$), and hand ($\Delta = +1.08$, $d = 0.52$, $p < 0.001$) subscores; the coordination/speed subscore did not change ($\Delta = +0.12$, $d = 0.07$, $p = 0.45$).

Table 3
Pre-post change in FMA-UE total and subscores (n = 112).

Subscale (max)	Pre (mean ± SD)	Post (mean ± SD)	Δ (mean ± SD)	p (paired t)	Cohen's d
Upper extremity (36)	13.43 ± 7.68	15.63 ± 8.61	+ 2.21 ± 3.19	< 0.001	0.69
Wrist (10)	1.96 ± 2.74	2.48 ± 3.19	+ 0.53 ± 1.29	< 0.001	0.41
Hand (14)	4.35 ± 4.18	5.43 ± 4.74	+ 1.08 ± 2.08	< 0.001	0.52
Coordination / speed (6)	1.88 ± 1.89	2.00 ± 1.97	+ 0.12 ± 1.62	0.45	0.07
FMA-UE total (66)	21.62 ± 14.38	25.55 ± 16.42	+ 3.94 ± 4.94	< 0.001	0.80

Baseline motor reserve and motor change

Patients with higher baseline FMA-UE scores showed larger observed pre-post increases, both descriptively and in a model relating post-intervention FMA-UE to baseline FMA-UE. Spearman correlation between baseline FMA-UE and Δ FMA-UE was $\rho = 0.34$ ($p = 0.0002$). The ANCOVA-style model regressing post-intervention FMA-UE on baseline FMA-UE returned a slope of 1.09 (95% CI 1.03 to 1.16, intercept 1.93, $R^2 = 0.92$). The estimated slope of 1.09 exceeded 1 and its 95% CI excluded 1. This indicates that the observed post-intervention FMA-UE values increased by more than one point for each additional baseline FMA-UE point, corresponding to a positive association between baseline motor capacity and absolute pre-post change. The result does not, by itself, exclude regression to the mean or other sources of baseline-dependent change. Equivalently, the fitted model estimated an additional 0.09 points of absolute pre-post change for each additional baseline FMA-UE point relative to a constant absolute-change model.

Stratifying the cohort into the prespecified severity tertiles (severe 0–22; moderate 23–44; mild 45–66; Fig. 4) confirmed this pattern. Median Δ FMA-UE was + 1.0 in the severely affected tertile ($n = 68$; median baseline FMA = 12), + 5.0 in the moderately affected tertile ($n = 34$; median baseline = 32), and + 6.5 in the mildly affected tertile ($n = 10$; median baseline = 48). The overall difference across tertiles was significant (Kruskal-Wallis $H(2) = 10.59$, $p = 0.005$); in the Bonferroni-corrected post-hoc Mann-Whitney comparisons, one of the three pairwise contrasts reached significance. Change differed between the severe and the moderate tertile (adjusted $p = 0.0085$). Neither the moderate versus mild contrast (adjusted $p = 1.0$) nor the severe versus mild contrast (adjusted $p = 0.19$) reached significance, the latter despite the largest difference in medians, which is compatible with the small size of the mild tertile ($n = 10$). Time since stroke did not differ detectably across the three severity tertiles (Kruskal-Wallis $H(2) = 1.45$, $p = 0.48$). Within this analysis, the observed differences in change across severity tertiles were therefore not accompanied by evidence of different distributions of time since stroke between the tertiles. This does not exclude residual confounding or other explanations for the baseline-change association.

Table 4

Distribution of relative improvement (Δ FMA-UE / baseline FMA-UE; $n = 111$). One patient with a baseline FMA-UE of 0 is excluded, as relative change is undefined. Percentages are of 111. The "no benefit" category ($\Delta \leq 0$) comprises the 16 patients with a small numerical worsening and the 13 unchanged patients reported in the text.

Category	n (%; 95% CI)
No benefit ($\Delta \leq 0$)	29 (26.1; 95% CI 18.9–35.0)
$\leq 25\%$ improvement	46 (41.4; 95% CI 32.7–50.7)
> 25 to $\leq 50\%$	20 (18.0; 95% CI 12.0–26.2)
> 50 to $\leq 75\%$	9 (8.1; 95% CI 4.3–14.7)
$> 75\%$	7 (6.3; 95% CI 3.1–12.4)

Predictors of motor change: multivariable analysis

A multivariable linear regression was fitted with Δ FMA-UE as the outcome and the prespecified predictor set (baseline FMA-UE, age at treatment, time since stroke, sex, stroke type, care pathway, affected hemisphere). Collinearity among predictors was negligible (all VIF < 1.2). The overall model was not significant ($F(7, 104) = 1.46$, $p = 0.19$, $R^2 = 0.09$, adjusted $R^2 = 0.03$), reflecting the substantial unexplained inter-individual variability in motor change. Within this overall non-significant model, only baseline FMA-UE reached the conventional threshold ($\beta = 0.09$ per point of baseline FMA, 95% CI 0.03 to 0.16, $p = 0.006$). Age ($\beta = 0.003$, $p = 0.94$), time since stroke ($\beta = -0.008$ per year, $p = 0.95$), sex ($\beta = -0.57$, $p = 0.56$), stroke type (hemorrhagic vs ischemic, $\beta = -0.04$, $p = 0.97$), care pathway (neurorehabilitation program vs standard prescription, $\beta = -0.25$, $p = 0.79$), and affected hemisphere (left vs right hemiparesis, $\beta = -1.17$, $p = 0.25$) were not associated with the magnitude of motor change. Given the non-significant overall model fit, the baseline-FMA finding should be interpreted as descriptive and not as a confirmed predictive relationship; it is, however, consistent with the ANCOVA-based baseline-conditional analysis described above.

Care pathway

The two care pathways were compared post hoc. Change in FMA-UE was similar in the outpatient neurorehabilitation program and in the standard prescription pathway ($+ 3.81 \pm 4.61$ versus $+ 4.07 \pm 5.30$ points; difference $- 0.27$, 95% CI $- 2.13$ to $+ 1.60$; Mann-Whitney $p = 0.92$), as was the proportion of patients reaching the 5-point threshold (24 of 57, 42.1%, versus 24 of 55, 43.6%; Fisher exact $p = 1.00$). Change in the modified Ashworth-derived scores did not differ at any joint segment (all Mann-Whitney $p \geq 0.49$; the largest absolute difference was 0.09 points, at the forearm), nor did change in contralesional RMT (difference $- 0.88$, 95% CI $- 2.49$ to $+ 0.74$; $p = 0.36$). After adjustment for baseline FMA-UE the difference in FMA-UE change was $- 0.40$ (95% CI $- 2.20$ to $+ 1.40$), and after additional adjustment for treatment period it was $- 1.11$ (95% CI $- 3.02$ to $+ 0.79$). Grip strength was not compared between the pathways, because it was introduced into the routine protocol in 2023 and 41 of the 53 available measurements come from the neurorehabilitation pathway. These confidence intervals exclude a between-pathway difference of the size of the 5-point threshold in either direction; the comparison is nevertheless confounded on several axes and is reported as descriptive.

Spasticity score reduction and motor improvement

Reductions in spasticity scores at the shoulder were modestly associated with FMA-UE improvement (Spearman $\rho = 0.19$, $p = 0.04$, $n = 111$). At other joints the associations were weaker and did not reach significance (elbow $\rho = 0.04$, $p = 0.68$; forearm $\rho = 0.16$, $p = 0.09$; wrist $\rho = 0.16$, $p = 0.09$; finger $\rho = 0.09$, $p = 0.36$; thumb $\rho = 0.14$, $p = 0.15$). Across the cohort, therefore, spasticity score change and motor-impairment change were only weakly correlated, consistent with partial dissociation between the two outcome domains. The same dissociation was present among the patients who did not improve: of the 16 patients with a numerical decrease in FMA-UE and the 19 with an increase in the shoulder score, only two appeared in both groups, against 2.7 expected under independence (Fisher exact $p = 0.73$), so the two forms of numerical worsening did not identify a common subgroup of patients.

Grip strength

In the subgroup of 53 patients in whom grip strength data were obtained, grip strength in the affected hand changed from $15.7 \pm 19.1\%$ to $16.9 \pm 19.0\%$ of the unaffected hand, a mean change of $+1.2 \pm 11.5\%$ (95% CI -1.9 to $+4.4$; $t(52) = 0.79$, $p = 0.44$; Cohen's $d = 0.11$; Wilcoxon $p = 0.57$). The median change was 0, with an IQR of -2.8 to $+5.1$, indicating broad inter-individual variability and no systematic group-level change. Change in grip strength was not significantly associated with reduction in spasticity scores at the shoulder, elbow, or wrist (all $p \geq 0.37$), nor with change in FMA-UE ($\rho = 0.10$, $p = 0.46$).

Contralesional corticospinal excitability

Contralesional RMT increased from $48.75 \pm 9.30\%$ MSO at baseline to $49.89 \pm 9.65\%$ MSO post-intervention, a mean change of $+1.14 \pm 4.32\%$ MSO (95% CI $+0.34$ to $+1.94$; $t(111) = 2.80$, $p = 0.006$; Cohen's $d = 0.27$; Wilcoxon $p = 0.0003$; $r = 0.35$). Pre- and post-intervention values were strongly correlated within patients (Pearson $r = 0.90$, $p < 0.001$), reflecting high within-subject test-retest consistency (Fig. 5). The direction of the small group-level change is consistent with reduced excitability of the rTMS-targeted hemisphere, in line with the intended mechanism of low-frequency stimulation; the magnitude is modest.

Δ RMT was not associated with any clinical outcome at the individual level. Δ FMA-UE ($\rho = 0.01$, $p = 0.92$), Δ shoulder mAS ($\rho = 0.08$, $p = 0.43$), Δ elbow mAS ($\rho = -0.02$, $p = 0.87$), Δ wrist mAS ($\rho = -0.13$, $p = 0.19$), Δ finger mAS ($\rho = 0.14$, $p = 0.15$), and Δ grip strength ($\rho = 0.03$, $p = 0.86$) all showed no significant relationship with the contralesional excitability change. Baseline RMT also did not predict subsequent FMA-UE improvement ($\rho = 0.05$, $p = 0.62$).

Chronicity and treatment response

Across the cohort, time since stroke was not associated with the magnitude of treatment-related change in any outcome. Linear regression of Δ FMA-UE on years since stroke was not significant ($F(1, 110) = 0.21$, $p = 0.65$, $R^2 = 0.002$; $\beta = -0.06$ points per year, 95% CI -0.33 to $+0.20$). Spearman correlations between time since stroke and mAS change were small and non-significant at every joint (shoulder $\rho = -0.15$, $p = 0.11$; elbow $\rho = -0.08$, $p = 0.42$; wrist $\rho = -0.07$, $p = 0.50$; finger $\rho = -0.07$, $p = 0.44$; thumb $\rho = 0.01$, $p = 0.93$; forearm $\rho = -0.03$, $p = 0.79$). The 8 patients in the late-subacute window (less than one year post-stroke) did not show systematically larger or smaller changes than the rest of the cohort, although the small subgroup size precludes formal statistical comparison, so that this is reported as a descriptive observation only (Fig. 6). Within the range of time since

stroke represented in this treated cohort, the data did not provide evidence of a linear association between chronicity and the magnitude of observed pre-post change. This analysis evaluates variation in observed pre-post change within a single treated cohort. It does not estimate the causal effect of time since stroke on treatment response and does not compare treatment effects between chronic and subacute patients under controlled conditions.

Discussion

Unlike the selected cohorts of many controlled rTMS trials, this series comprised 112 patients with chronic stroke who completed a routine outpatient treatment program at a specialized rTMS service. Modified Ashworth-derived scores decreased at every assessed joint segment and remained significant after correction for the six prespecified comparisons. FMA-UE increased by about four points, scaling with baseline motor reserve. Grip strength in the affected hand did not change, and contralesional resting motor threshold increased slightly without tracking any clinical outcome.

Because the cohort has no sham comparator, the contribution of the stimulation component cannot be disentangled from that of the adjunctive therapy delivered in both care pathways, from non-specific effects of repeated structured engagement, or from expectation and repeated-assessment effects. No patient was excluded from the analyzed cohort on the basis of observed treatment response.

Spasticity scores showed the most directionally consistent pre-post change

This directional consistency is unusual. Trials of rTMS for post-stroke spasticity exist, but they remain small and methodologically heterogeneous. A recent systematic review of 26 randomized trials, 14 of them in stroke, reported sample sizes of 14 to 60 participants and heterogeneity sufficient to preclude meta-analysis (24). In a sham-controlled trial in chronic stroke, contralesional 1 Hz rTMS combined with physiotherapy reduced wrist spasticity relative to sham (between-group $p = 0.03$), whereas motor gains did not differ between groups (43). Pooled meta-analytic estimates likewise show small-to-moderate spasticity reductions (22, 44), although superiority over sham has not been demonstrated consistently across all pooled comparisons (45).

The distribution-based minimal clinically important differences for the Modified Ashworth Scale were derived in a cohort of 115 patients with stroke followed over six months (41), using the same recoding of the 1 + grade; the lower of the two thresholds is recommended when impairment is severe and the expected gain is small, as in 61% of this cohort. Measured against it, 39.6% of patients here improved by at least 0.48 points, whereas 23.5% of the derivation cohort exceeded the same threshold during that period. That figure counts change in either direction and is therefore not directly comparable; the derivation work also rated flexors alone, while the composite used here averages two opposing directions per joint.

Spasticity reflects disordered supraspinal regulation of spinal reflex circuitry, mediated by cortical, brainstem, and spinal networks beyond the corticospinal tract (23, 28–30); on this view, contralesional low-frequency rTMS could influence tone-regulating networks without requiring measurable restoration of corticospinal output (46). The present data did not test reticulospinal or corticoreticular mechanisms directly, but the reduction in

spasticity scores occurred without corresponding FMA-UE or contralesional RMT change and without a chronicity association.

The baseline-to-change associations observed for the modified Ashworth-derived scores are compatible with regression to the mean, which this design cannot exclude. The consistent direction of the changes across the six joint segments and their persistence after Bonferroni correction make a purely chance-based explanation less plausible, although shared rater or expectation effects remain possible.

Motor improvement is real but small, and scales with motor reserve

The mean FMA-UE gain of + 3.94 points (95% CI 3.02 to 4.85) is at the upper end of the pooled adjunctive benefit of rTMS over conventional rehabilitation alone reported in a recent meta-analysis of mixed stroke populations (MD 3.04 points, 95% CI 1.16 to 4.92) (47). Meta-analytic evidence specific to chronic stroke is less consistent. In patients more than six months post-stroke, one meta-analysis found no significant effect on FMA-UE (SMD 0.13, 95% CI - 0.11 to 0.36) (9). A network meta-analysis across stroke phases estimated larger, protocol-dependent differences of approximately 5 to 9 FMA-UE points versus sham stimulation (48). In the present cohort, 43% of patients reached a change of ≥ 5 points, which lies within the 4.25-7.25-point MCID range reported by Page and colleagues in people with minimal to moderate impairment due to chronic stroke (42). Because the MCID values proposed by Page and colleagues were derived from patients with mild-to-moderate chronic impairment, their applicability to the severely affected tertile of our cohort (61%) is uncertain. Comparison with usual care provides little information at this stage because spontaneous recovery is concentrated in the first three months after stroke (49), whereas this cohort was treated at a median of three years after onset; beyond the subacute phase, usual-care gains continue only at a substantially slower rate (49).

A clinically more relevant finding concerns the relationship between baseline motor reserve and change. The standard descriptive correlation between baseline FMA-UE and Δ FMA-UE is open to a regression-to-mean interpretation. The ANCOVA-style post-on-pre model indicated a modest but statistically reliable tendency for higher-baseline patients to gain slightly more, opposite to the regression-to-the-mean pattern. The multivariable regression pointed in the same direction, but its overall fit was not significant, so it is reported as exploratory and its individual coefficients, baseline FMA-UE included, are not interpreted as independent predictor effects. Most inter-individual variability in change of motor function is not explained by routinely documented clinical variables, a familiar finding in chronic stroke neuromodulation cohorts (4).

The gains in FMA-UE were carried primarily by the proximal-arm, wrist, and hand subscores, with the coordination/speed subscore essentially flat ($d = 0.07$). The pattern is more consistent with improved access to existing motor capacity than with restoration of higher-order coordination. This pattern is consistent with residual output relying increasingly on non-corticospinal descending pathways. After severe corticospinal damage, upregulated reticulospinal activity can support proximal and within-synergy movements, whereas out-of-synergy movements and finger fractionation remain poor (29). The persistence of these distal deficits most plausibly explains why the overall FMA-UE gain remained moderate. The interpretation aligns with mechanistic accounts in which contralesional inhibitory rTMS can facilitate output from the ipsilesional hemisphere when residual corticospinal substrate is available, but cannot create that substrate where it has been lost (26, 48, 50).

On this account, baseline FMA-UE may act partly as a proxy for preserved corticospinal tract integrity (51), so the baseline-conditional gradient could reflect the amount of corticospinal substrate available for facilitation instead of a severity effect per se. In the severe tertile ($n = 68$, 61% of the cohort) the median gain was + 1.0 FMA-UE point, below the 5-point threshold applied here. Given the amplified intraindividual variability of motor performance in stroke survivors (52), a group-level change of this magnitude could not be attributed to the stimulation by the present design.

Phenotype-stratified response patterns and the limit of one-protocol-fits-all

The pattern of baseline-conditional response observed here aligns with the bimodal balance-recovery model (26) and with recent operationalizations of phenotype-based rTMS selection. The START framework (53) uses the upper-extremity Fugl-Meyer score as its primary decision point, with a criterion of 42/66. In an exploratory crossover study of 24 patients, 11 of 12 participants above this threshold improved more with inhibitory contralesional M1 rTMS, whereas 10 of 12 at or below it improved more with facilitatory rTMS over the contralesional dorsal premotor cortex. A secondary criterion based on corticospinal tract integrity further refined the classification, and the authors describe the algorithm as preliminary. In the present cohort, 88% of patients (99/112) had a baseline FMA-UE at or below this threshold (median 17, IQR 11–32).

On phenotype-stratified frameworks, the majority of our cohort is not the population for which an inhibitory contralesional M1 rTMS protocol would have been the predicted match, yet it showed a consistent spasticity score reduction across joints regardless. This dissociation is what a stratification-based framework predicts, not an anomaly; it reinforces the case for phenotype-aware trial designs in chronic stroke neuromodulation. If 88% of the cohort lies outside the corticospinal-facilitation phenotype but the spasticity reduction is uniform across this same majority, then any stimulation-specific contribution to spasticity is more likely to operate through pathways other than corticospinal facilitation, consistent with the supraspinal tone-regulation account discussed above.

Chronicity is not the dominant moderator

Across a range from three months to twenty-one years since stroke, neither motor nor spasticity score outcomes were significantly associated with time since stroke in any analysis, and the 95% confidence interval of the observed slope (-0.33 to $+0.20$ FMA-UE points per year) excludes a chronicity gradient of the size of the 5-point MCID per decade in either direction. These findings are consistent with evidence that domain-specific neuroplastic responsiveness persists into late chronic stages (31–33, 51), and they argue against using time since stroke as an exclusion criterion in clinical or trial decisions about contralesional rTMS; the window of heightened responsiveness for motor training in the early subacute period (27) does not imply the absence of treatment-responsive plasticity later for the outcome domains described here.

The cohort is nevertheless observational, time since stroke is concentrated in the 1- to 6-year range, and only five patients fall beyond ten years, so the absence of a measurable chronicity effect may reflect the limited resolution of this cohort more than a true absence of any effect.

Corticospinal excitability change does not track clinical change

Contralesional RMT increased slightly post-intervention (+ 1.1% MSO, $d = 0.27$), in the direction predicted by the inhibitory effect of low-frequency stimulation on the targeted hemisphere, where 1 Hz rTMS raises the resting motor threshold in healthy volunteers (54), but did not correlate with any clinical outcome at the individual level, and baseline RMT did not predict motor improvement. RMT is a coarse index of corticospinal excitability that fluctuates with the subject's momentary state and attention (55), and its prognostic value differs by hemisphere. Ipsilesional RMT correlates with motor function in most but not all studies, whereas changes in contralesional RMT have shown no significant association with hand motor recovery (56, 57). The small group-level shift observed here may partly reflect such non-specific factors. That RMT change did not track clinical change cautions against its use as a surrogate for clinical response in this setting.

Limitations

The most fundamental constraint is that the design is a retrospective observational cohort without a control arm, which shapes the inferences that can be drawn from it. Stimulation-specific effects cannot be disentangled from those of the concurrent therapeutic sessions, from non-specific effects of repeated structured engagement with a specialized clinic, or from expectation and placebo effects. The pattern of findings, namely uniform spasticity score reduction across joints, motor change scaled to baseline reserve, and no chronicity association, is internally consistent and broadly aligns with directionally similar findings in sham-controlled trials (22, 58, 43), but causal attribution to the stimulation component requires a controlled comparison.

Second, as described in the Methods, full and uniform blinding could not be guaranteed throughout. While most outcomes used here are at least partly objective (FMA-UE scoring is rule-based; grip strength is instrument-based; RMT is an objective stimulator-output threshold), the modified Ashworth Scale is examiner-dependent and ordinal, with rater identity shown to be a major determinant of Ashworth-type scores (59), and unblinded assessment in the subset where blinding could not be maintained cannot be ruled out as a source of optimistic bias for that outcome. Objective, instrumented measurement of resistance to externally induced joint movement, such as hand-held dynamometry of the wrist in chronic stroke (60), would replace the examiner's subjective grading with instrumented torque and EMG readouts and should be considered for prospective work, although inter-rater reliability remains to be established. The consistency of mAS changes across six segments and their lack of association with FMA-UE changes argue against uniform expectation-driven bias, but do not exclude it. Because the instruments measure different constructs, this lack of association does not validate the mAS reductions.

Third, the cohort is subject to selection at several stages of the care pathway. Patients had to become aware of the specialized service, travel to the clinic, attend regularly over several weeks, and sustain the demands through to completion; patients unable to meet these requirements are unlikely to be represented. Most patients reached the clinic through self-referral, with only a small minority referred by community-based physicians or other rehabilitation services. Because a pre-screening log was not maintained, the size of this informational and geographic filter cannot be quantified, and generalizability remains restricted to patients who became aware of the specialized TMS service and were able to reach it.

Fourth, several methodological constraints apply to specific outcomes. Modified Ashworth-derived joint scores were constructed as described in the Methods and applied consistently at both time points, but the composite

scores should be interpreted as a study-specific operationalization of resistance to passive movement and not as a direct quantitative measure of spasticity. Surface EMG was not available, so contralesional RMT was determined visually and not by the EMG-based criterion; absolute threshold values cannot be compared to EMG-based studies, and small effect sizes such as the + 1.14% MSO change should be interpreted accordingly. Visual determination yields systematically higher threshold estimates than EMG-based determination, on average 11.3% higher in healthy subjects (40), so stimulation at 120% of the visually determined threshold likely exceeded 120% of an EMG-based threshold. The same procedure at both time points by the same assessors leaves within-patient comparisons and relative dosing consistency unaffected, but absolute intensity is not equivalent to EMG-titrated protocols. No serious adverse events were observed at this intensity.

A further technical constraint arises from the change of stimulation system during the observation period, with 27 patients treated with a Nexstim NBT System 2 until December 2021 and 85 with a Magstim Horizon from January 2022. Stimulation site, frequency, pulse number, and intensity relative to the individually determined resting motor threshold were identical across both systems, but the two devices differ in pulse waveform and in the navigation principle. A comparison of the two periods is reported in Additional File 2: change in FMA-UE and in modified Ashworth-derived scores was smaller in the earlier period, whereas change in resting motor threshold was almost identical. Because the stimulation system is completely confounded with calendar period, these differences can be described but cannot be attributed to the device. The two care pathways are confounded with calendar period in the same way, since 22 of the 27 patients treated in the earlier period followed the standard outpatient prescription pathway, whereas 52 of the 85 patients treated later were enrolled in the outpatient neurorehabilitation program. The pathways further differ in adjunctive therapy, session number, treatment duration, cumulative pulse count, and concurrent rehabilitation. The pathway comparison reported in the Results is therefore descriptive and cannot isolate the contribution of any of these components, and the absence of a detectable difference should not be read as evidence that the two pathways are equivalent.

Last among the methodological constraints, motor and spasticity scores capture state more than trait. Both motor output and corticospinal excitability fluctuate with recent physical exertion (61, 62) and limb temperature (63). In stroke survivors, motor performance shows amplified trial-to-trial variability within a single session (52, 64), and comorbid sleep disorders are associated with poorer functional recovery and greater disability (64). None of these factors was systematically controlled, so a numerical worsening at the post-intervention assessment may reflect short-term within-patient variability, not sustained deterioration, across the treatment course. The pattern of the observed decreases supports this reading. Of the 41 FMA-UE points lost across the 16 patients with a decrease, 22 were accounted for by the coordination/speed subscore, the only subscore without a group-level change, and the increases in the modified Ashworth-derived scores were in most cases confined to a single grade step in a single movement direction. This account does not extend to the three patients whose FMA-UE decreased by 5 points or more, for whom the present design cannot determine whether the decrease reflects measurement variability or genuine deterioration.

Fifth, the durability of the observed changes beyond the immediate post-treatment assessment was not systematically captured. Follow-up data are available for a few patients through subsequent clinical visits but are not analyzed here. The question of how long the observed clinical effects persist after the stimulation course ends, and whether maintenance or booster stimulation would be needed, remains open.

Finally, multiplicity was controlled within the prespecified mAS family but not across the broader exploratory analyses (ANCOVA, multivariable regression, severity-tertile post-hoc tests, FMA-UE subscores, cross-domain Spearman correlations). P-values from these analyses are descriptive.

Taken together, these limitations define the present analysis as a hypothesis-generating description of pre-post change during a routine multimodal treatment episode. It is not evidence of efficacy attributable to rTMS. Its principal value lies in characterizing the distribution and consistency of observed changes across clinical and physiological measures and in generating testable hypotheses for future controlled studies, e.g., suggesting spasticity as a candidate primary endpoint for future controlled work and supporting the design and development of stratified trials in chronic stroke neuromodulation.

Conclusions

In this cohort of chronic stroke patients, the guideline-recommended contralesional 1 Hz rTMS protocol and its standardized pre- and post-intervention assessment were delivered within a routine outpatient service, and within this setting, the observed pre-post changes differed between outcome domains. Spasticity score reduction was more consistent across patients and across joints than voluntary motor improvement, which was smaller and concentrated in patients with greater residual motor capacity. The reduction was directionally uniform across six joint segments, remained significant after correction for multiple comparisons, dissociated from changes in contralesional corticospinal excitability, and was independent of time since stroke. FMA-UE changes were smaller in absolute magnitude than the changes observed in the modified Ashworth-derived scores and were positively associated with baseline FMA-UE scores. The observed increase was concentrated in the upper-extremity, wrist, and hand subscores. No clear linear association between time since stroke and the magnitude of observed pre-post change in either outcome was detected within the range represented in this cohort.

These uncontrolled findings cannot establish efficacy or attribute the observed changes specifically to rTMS, but they nevertheless suggest two directions for the further evaluation and clinical use of contralesional 1 Hz rTMS in chronic stroke. First, future controlled trials in this population should assess spasticity-related outcomes alongside motor impairment and functional outcomes using validated and clinically interpretable measures. The spasticity finding is compatible with mechanistic hypotheses involving supraspinal regulation of muscle tone and was observed in a clinically heterogeneous cohort that included many patients with severe baseline motor impairment. Second, a long interval since stroke does not by itself identify patients who are unlikely to change and should therefore not serve as an a priori exclusion criterion for rTMS within this treatment pathway. Within this treated cohort, no clear linear association between time since stroke and the magnitude of observed pre-post change was detected, although the study was not designed to compare treatment effects across chronicity strata.

Declarations

Ethics approval and consent to participate.

The analysis was approved by the Ethics Committee of the Medical Faculty of Eberhard Karls University Tübingen and the University Hospital Tübingen (reference 2026 – 0203) and was conducted in accordance with

the Declaration of Helsinki. Written informed consent for treatment and for the use of clinical data for retrospective research was obtained from each patient. Study-specific informed consent was waived under the approved protocol.

Consent for publication.

Not applicable. The manuscript reports fully anonymized group-level data; no individual-level identifying information is presented.

Competing interests.

The authors have no competing interests to declare that are relevant to the content of this article.

Funding.

No specific funding was received for the present retrospective analysis. The rTMS outpatient program is operated as part of routine clinical care.

Author Contribution

AL conducted medical screening, assessment of eligibility and contraindications, selection of treatment protocols, post-treatment clinical evaluations, conceived and designed the analysis, curated and analyzed the data, interpreted the results, and drafted and revised the manuscript. CR contributed to clinical data acquisition, data curation and data analysis. CKD performed clinical and neurophysiological assessments. PM supervised and reviewed the data analysis. JL advised on the procedures in the outpatient clinic and reviewed the manuscript. DH, AJ, LRJ, WM, and GK supported medical screening, assessment of eligibility and contraindications, selection of treatment protocols, post-treatment clinical evaluations and reviewed the manuscript. UZ supervised the project and reviewed and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgement

The authors thank the clinical staff of the rTMS outpatient clinic at the Department of Neurology and Stroke for their consistent delivery of the standardized protocol over seven years, and the occupational and physiotherapy teams of the University Center for Physiotherapy and the Center for Outpatient Rehabilitation (ZAR) Tübingen for adjunctive treatment. We are grateful to all patients who consented to the retrospective use of their clinical data.

Data Availability

The de-identified dataset and the analysis scripts that support the findings of this study are available from the corresponding author on reasonable request, subject to approval by the Ethics Committee of the Medical

References

1. Feigin VL, Abate MD, Abate YH, Abd ElHafeez S, Abd-Allah F, Abdelalim A, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol.* 2024;23(10):973–1003. 10.1016/S1474-4422(24)00369-7.
2. Broeks JG, Lankhorst GJ, Rumping K, Prevo AJH. The long-term outcome of arm function after stroke: results of a follow-up study. *Disabil Rehabil.* 1999;21(8):357–64. 10.1080/096382899297459.
3. Harvey RL, Edwards D, Dunning K, Fregni F, Stein J, Laine J, et al. Randomized Sham-Controlled Trial of Navigated Repetitive Transcranial Magnetic Stimulation for Motor Recovery in Stroke: The NICHE Trial. *Stroke.* 2018;49(9):2138–46. 10.1161/STROKEAHA.117.020607.
4. Hofmeijer J, Ham F, Kwakkel G. Evidence of rTMS for Motor or Cognitive Stroke Recovery: Hype or Hope? *Stroke.* 2023;54(10):2500–11. 10.1161/STROKEAHA.123.043159.
5. Smith MC, Stinear CM. Transcranial magnetic stimulation (TMS) in stroke: Ready for clinical practice? *J Clin Neurosci.* 2016;31:10–4. 10.1016/j.jocn.2016.01.034.
6. Rithiely B, Shirahige L, Lima P, Souza M, Marques D, Brito R, et al. Non-invasive brain stimulation for stroke-related motor impairment and disability: an umbrella review of systematic review and meta-analysis. *Front Neurosci.* 2025;19:1633986. 10.3389/fnins.2025.1633986.
7. Aderinto N, Olatunji G, Kokori E, Agbo CE, Babalola AE, Aboje JE, et al. Clinical Applications of Non-Invasive Brain Stimulation in Stroke Recovery: A Review of Current Evidence and Therapeutic Strategies. *Curr Treat Options Neurol.* 2025;27(1):8. 10.1007/s11940-024-00823-5.
8. Fisicaro F, Lanza G, Grasso AA, Pennisi G, Bella R, Paulus W, et al. Repetitive transcranial magnetic stimulation in stroke rehabilitation: review of the current evidence and pitfalls. *Ther Adv Neurol Disord.* 2019;12:1756286419878317. 10.1177/1756286419878317.
9. Xie G, Wang T, Deng L, Zhou L, Zheng X, Zhao C, et al. Repetitive transcranial magnetic stimulation for motor function in stroke: a systematic review and meta-analysis of randomized controlled studies. *Syst Rev.* 2025;14(1):47. 10.1186/s13643-025-02794-3.
10. Rektorová I, Pupíková M, Fleury L, Brabenec L, Hummel FC. Non-invasive brain stimulation: current and future applications in neurology. *Nat Rev Neurol.* 2025;21(12):669–86. 10.1038/s41582-025-01137-z.
11. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol.* 2004;55(3):400–9. 10.1002/ana.10848.
12. Grefkes C, Ward NS. Cortical reorganization after stroke: how much and how functional? *Neuroscientist.* 2014;20(1):56–70. 10.1177/1073858413491147.
13. Nowak DA, Grefkes C, Ameli M, Fink GR. Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. *Neurorehabil Neural Repair.* 2009;23(7):641–56. 10.1177/1545968309336661.
14. Takeuchi N, Izumi SI. Noninvasive Brain Stimulation for Motor Recovery after Stroke: Mechanisms and Future Views. *Stroke Res Treat.* 2012;584727. 10.1155/2012/584727.

15. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). *Clin Neurophysiol.* 2020;131(2):474–528. 10.1016/j.clinph.2019.11.002.
16. Fugl-Meyer A, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *J Rehabil Med.* 1975;7(1):13–31. 10.2340/1650197771331.
17. Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. *Clin Rehabil.* 2005;19(4):404–11. 10.1191/0269215505cr832oa.
18. Bushnell C, Bettger JP, Cockcroft KM, Cramer SC, Edelen MO, Hanley D, et al. Chronic Stroke Outcome Measures for Motor Function Intervention Trials: Expert Panel Recommendations. *Circ Cardiovasc Qual Outcomes.* 2015;8. 10.1161/CIRCOUTCOMES.115.002098.
19. Shim J, Kim C. Effects of Navigated rTMS on Post-Stroke Upper-Limb Function: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Brain Sci.* 2025;15(11):1247. 10.3390/brainsci15111247.
20. Pundik S, McCabe J, Skelly M, Tatsuoka C, Daly JJ. Association of spasticity and motor dysfunction in chronic stroke. *Ann Phys Rehabil Med.* 2019;62(6):397–402. 10.1016/j.rehab.2018.07.006.
21. Zeng H, Chen J, Guo Y, Tan S. Prevalence and Risk Factors for Spasticity After Stroke: A Systematic Review and Meta-Analysis. *Front Neurol.* 2021;11:616097. 10.3389/fneur.2020.616097.
22. Wang X, Ge L, Hu H, Yan L, Li L. Effects of Non-Invasive Brain Stimulation on Post-Stroke Spasticity: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Brain Sci.* 2022;12(7):836. 10.3390/brainsci12070836.
23. Chen B, Yang T, Liao Z, Sun F, Mei Z, Zhang W. Pathophysiology and Management Strategies for Post-Stroke Spasticity: An Update Review. *Int J Mol Sci.* 2025;26(1):406. 10.3390/ijms26010406.
24. Iacona M, Ferlito R, Bella R, Cantone M, Ferri R, Fisicaro F, et al. Repetitive Transcranial Magnetic Stimulation for Spasticity in Stroke and Other Neuromotor Disorders: A Systematic Review of Randomized Clinical Trials. *J Clin Med.* 2026;15(5):1932. 10.3390/jcm15051932.
25. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting Neurorehabilitation Right: What Can Be Learned From Animal Models? *Neurorehabil Neural Repair.* 2012;26(8):923–31. 10.1177/1545968312440745.
26. Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat Rev Neurol.* 2014;10(10):597–608. 10.1038/nrneurol.2014.162.
27. Dromerick AW, Geed S, Barth J, Brady K, Giannetti ML, Mitchell A, et al. Critical Period After Stroke Study (CPASS): A phase II clinical trial testing an optimal time for motor recovery after stroke in humans. *Proc Natl Acad Sci.* 2021;118(39):e2026676118. 10.1073/pnas.2026676118.
28. Qin Y, Liu X, Zhang Y, Wu J, Wang X. Effects of transcranial combined with peripheral repetitive magnetic stimulation on limb spasticity and resting-state brain activity in stroke patients. *Front Hum Neurosci.* 2023;17:992424. 10.3389/fnhum.2023.992424.
29. Mooney RA, Anaya MA, Stilling JM, Celnik PA. Heightened Reticulospinal Excitability after Severe Corticospinal Damage in Chronic Stroke. *Ann Neurol.* 2025;97(1):163–74. 10.1002/ana.27103.

30. Schading-Sassenhausen S, Dietz V, Freund P. Effect of corticospinal and reticulospinal tract damage on spastic muscle tone and mobility: a retrospective observational MRI study. *eBioMedicine*. 2025;118:105824. 10.1016/j.ebiom.2025.105824.
31. Ward NS. Restoring brain function after stroke - bridging the gap between animals and humans. *Nat Rev Neurol*. 2017;13(4):244–55. 10.1038/nrneurol.2017.34.
32. Bashir S, Vernet M, Najib U, Perez J, Alonso-Alonso M, Knobel M, et al. Enhanced motor function and its neurophysiological correlates after navigated low-frequency repetitive transcranial magnetic stimulation over the contralesional motor cortex in stroke. *Restor Neurol Neurosci*. 2016;34(4):677–89. 10.3233/RNN-140460.
33. Su F, Xu W. Enhancing Brain Plasticity to Promote Stroke Recovery. *Front Neurol*. 2020;11:554089. 10.3389/fneur.2020.554089.
34. Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmüller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol*. 2021;132(1):269–306. 10.1016/j.clinph.2020.10.003.
35. Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. *Practitioner*. 1964;192:540–2. PubMed PMID: 14143329.
36. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*. 1987;67(2):206–7. 10.1093/ptj/67.2.206.
37. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil*. 1999;13(5):373–83. 10.1191/026921599677595404.
38. Bertrand AM, Fournier K, Wick Brasey MG, Kaiser ML, Frischknecht R, Diserens K. Reliability of maximal grip strength measurements and grip strength recovery following a stroke. *J Hand Ther*. 2015;28(4):356–62. 10.1016/j.jht.2015.04.004. quiz 363.
39. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol*. 2015;126(6):1071–107. 10.1016/j.clinph.2015.02.001.
40. Westin GG, Bassi BD, Lisanby SH, Luber B. Determination of motor threshold using visual observation overestimates transcranial magnetic stimulation dosage: Safety implications. *Clin Neurophysiol*. 2014;125(1):142–7. 10.1016/j.clinph.2013.06.187.
41. Chen CL, Chen CY, Chen HC, Wu CY, Lin KC, Hsieh YW, et al. Responsiveness and minimal clinically important difference of Modified Ashworth Scale in patients with stroke. *Eur J Phys Rehabil Med*. 2019;55(6):754–60. 10.23736/S1973-9087.19.05545-X.
42. Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. *Phys Ther*. 2012;92(6):791–8. 10.2522/ptj.20110009.
43. Barros Galvão SC, Borba Costa Dos Santos R, Borba Dos Santos P, Cabral ME, Monte-Silva K. Efficacy of Coupling Repetitive Transcranial Magnetic Stimulation and Physical Therapy to Reduce Upper-Limb

- Spasticity in Patients With Stroke: A Randomized Controlled Trial. *Arch Phys Med Rehabil.* 2014;95(2):222–9. 10.1016/j.apmr.2013.10.023.
44. Cao X, Xu W, Yu M. Age and method-specific differences in the efficacy of non-invasive brain stimulation in patients' post-stroke limb spasticity: a meta-analysis. *Neurol Asia.* 2024;29(4):985–1007. 10.54029/2024eiu.
 45. Xu P, Huang Y, Wang J, An X, Zhang T, Li Y, et al. Repetitive transcranial magnetic stimulation as an alternative therapy for stroke with spasticity: a systematic review and meta-analysis. *J Neurol.* 2021;268(11):4013–22. 10.1007/s00415-020-10058-4.
 46. Mahmoud W, Hultborn H, Zuluaga J, Zrenner C, Zrenner B, Ziemann U, et al. Testing spasticity mechanisms in chronic stroke before and after intervention with contralesional motor cortex 1 Hz rTMS and physiotherapy. *J Neuroeng Rehabil.* 2023;20(1):150. 10.1186/s12984-023-01275-9.
 47. Lee HY, Ryu B. Effects of Repetitive Transcranial Magnetic Stimulation on Upper and Lower Limb Motor Function and Spasticity After Stroke: A Meta-Analysis. *Brain Neurorehabilitation.* 2025;18(2):e5. 10.12786/bn.2025.18.e5.
 48. Xia Y, Xu Y, Li Y, Lu Y, Wang Z. Comparative Efficacy of Different Repetitive Transcranial Magnetic Stimulation Protocols for Stroke: A Network Meta-Analysis. *Front Neurol.* 2022;13:918786. 10.3389/fneur.2022.918786.
 49. Kolmos M, Munoz-Novoa M, Sunnerhagen K, Alt Murphy M, Kruuse C. Upper-extremity motor recovery after stroke: A systematic review and meta-analysis of usual care in trials and observational studies. *J Neurol Sci.* 2025;468:123341. 10.1016/j.jns.2024.123341.
 50. Avenanti A, Coccia M, Ladavas E, Provinciali L, Ceravolo MG. Low-frequency rTMS promotes use-dependent motor plasticity in chronic stroke: A randomized trial. *Neurology.* 2012;78(4):256–64. 10.1212/WNL.0b013e3182436558.
 51. Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain.* 2007;130(Pt 1):170–80. 10.1093/brain/awl333.
 52. Delmas S, Tiwari A, Tseng H, Poisson SN, Diehl M, Lodha N. Amplified Intraindividual Variability in Motor Performance in Stroke Survivors: Links to Cognitive and Clinical Outcomes. *Brain Behav.* 2025;15(2):e70365. 10.1002/brb3.70365.
 53. Lin YL, Potter-Baker KA, Sankarasubramanian V, Cunningham DA, Li M, O'Laughlin K, et al. Stratification algorithm for repetitive TMS in stroke (START): Results from an exploratory crossover study. *J Neurol Sci.* 2025;473:123478. 10.1016/j.jns.2025.123478.
 54. Fitzgerald P. Intensity-dependent effects of 1 Hz rTMS on human corticospinal excitability. *Clin Neurophysiol.* 2002;113(7):1136–41. 10.1016/S1388-2457(02)00145-1.
 55. Karabanov AN, Raffin E, Siebner HR. The Resting Motor Threshold – Restless or Resting? A Repeated Threshold Hunting Technique to Track Dynamic Changes in Resting Motor Threshold. *Brain Stimulat.* 2015;8(6):1191–4. 10.1016/j.brs.2015.07.001.
 56. Rosso C, Lamy JC. Does Resting Motor Threshold Predict Motor Hand Recovery After Stroke? *Front Neurol.* 2018;9:1020. 10.3389/fneur.2018.01020.
 57. Veldema J, Nowak DA, Gharabaghi A. Resting motor threshold in the course of hand motor recovery after stroke: a systematic review. *J Neuroeng Rehabil.* 2021;18(1):158. 10.1186/s12984-021-00947-8.

58. Gottlieb A, Boltzmann M, Schmidt SB, Gutenbrunner C, Krauss JK, Stangel M, et al. Treatment of upper limb spasticity with inhibitory repetitive transcranial magnetic stimulation: A randomized placebo-controlled trial. *NeuroRehabilitation*. 2021;49(3):425–34. 10.3233/NRE-210088.
59. Fleuren JFM, Voerman GE, Erren-Wolters CV, Snoek GJ, Rietman JS, Hermens HJ, et al. Stop using the Ashworth Scale for the assessment of spasticity. *J Neurol Neurosurg Psychiatry*. 2010;81(1):46–52. 10.1136/jnnp.2009.177071.
60. Mahmoud W, Haugland M, Ramos-Murguialday A, Hultborn H, Ziemann U. Measuring resistance to externally induced movement of the wrist joint in chronic stroke patients using an objective hand-held dynamometer. *Clin Neurophysiol Pract*. 2023;8:97–110. 10.1016/j.cnp.2023.05.001.
61. Samii A, Wassermann EM, Ikoma K, Mercuri B, Hallett M. Characterization of postexercise facilitation and depression of motor evoked potentials to transcranial magnetic stimulation. *Neurology*. 1996;46(5):1376–1376. 10.1212/WNL.46.5.1376.
62. Brasil-Neto JP, Pascual-Leone A, Valls-Solé J, Cammarota A, Cohen LG, Hallett M. Postexercise depression of motor evoked potentials: a measure of central nervous system fatigue. *Exp Brain Res*. 1993;93(1):181–4. 10.1007/BF00227794.
63. Ansari Y, Remaud A, Tremblay F. Modulation of corticomotor excitability in response to distal focal cooling. *PeerJ*. 2018;6:e6163. 10.7717/peerj.6163.
64. Fulk GD, Boyne P, Hauger M, Ghosh R, Romano S, Thomas J, et al. The Impact of Sleep Disorders on Functional Recovery and Participation Following Stroke: A Systematic Review and Meta-Analysis. *Neurorehabil Neural Repair*. 2020;34(11):1050–61. 10.1177/1545968320962501.

Figures

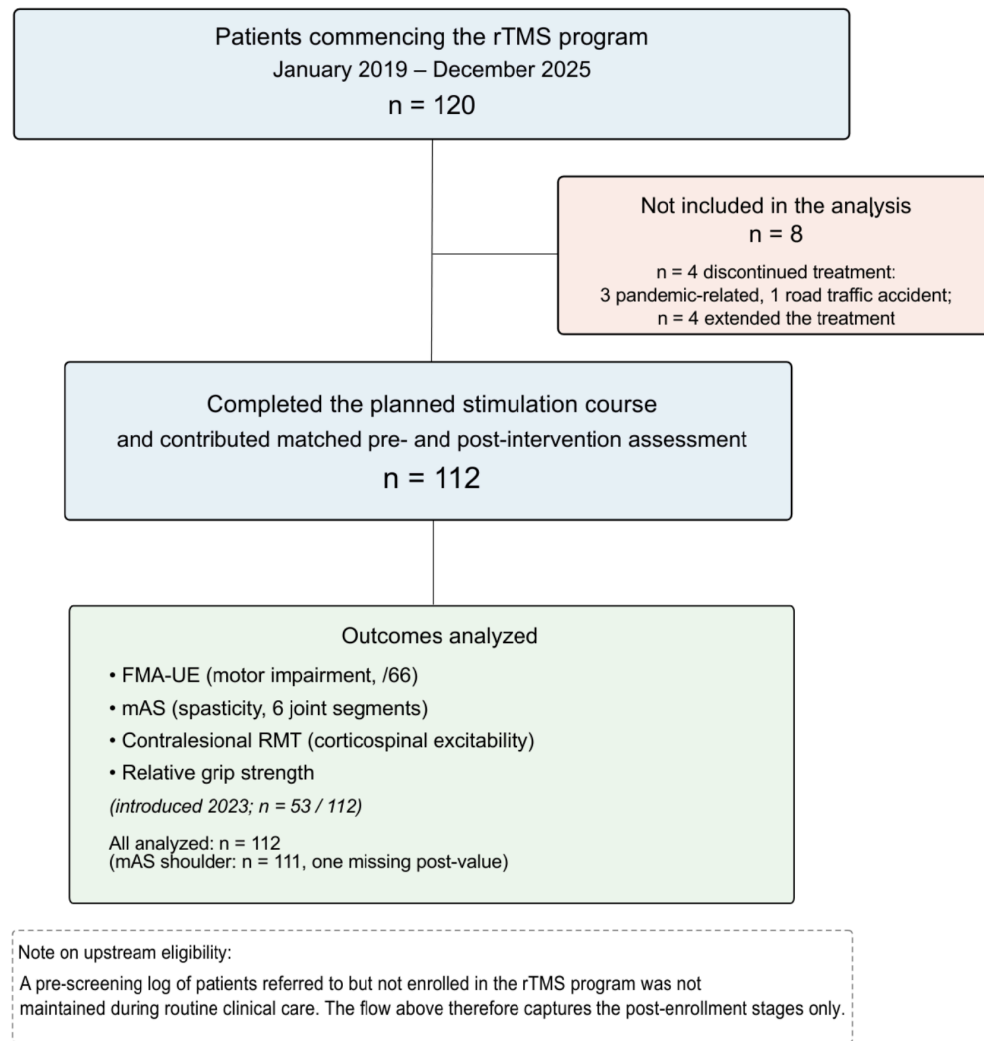


Figure 1

Flow diagram of patient enrollment, exclusion, and analysis in a retrospective cohort study of contralesional 1 Hz rTMS in chronic stroke (2019-2025). 120 consecutive patients treated with the contralesional 1 Hz protocol commenced the program during the observation period (January 2019 - December 2025); 8 did not contribute post-intervention assessments (4 discontinued due to intercurrent illness unrelated to rTMS, not stimulation-related adverse events; 4 received an extended treatment course without a completed post-intervention assessment). The remaining 112 patients completed the full stimulation course and form the analytical cohort. Routine clinical care did not include a pre-screening log of patients referred to but not enrolled, so the figure captures the post-enrollment flow only. Grip strength was introduced into the routine protocol in 2023 and is available for the most recent 53 patients (missing-at-design, not response-related).

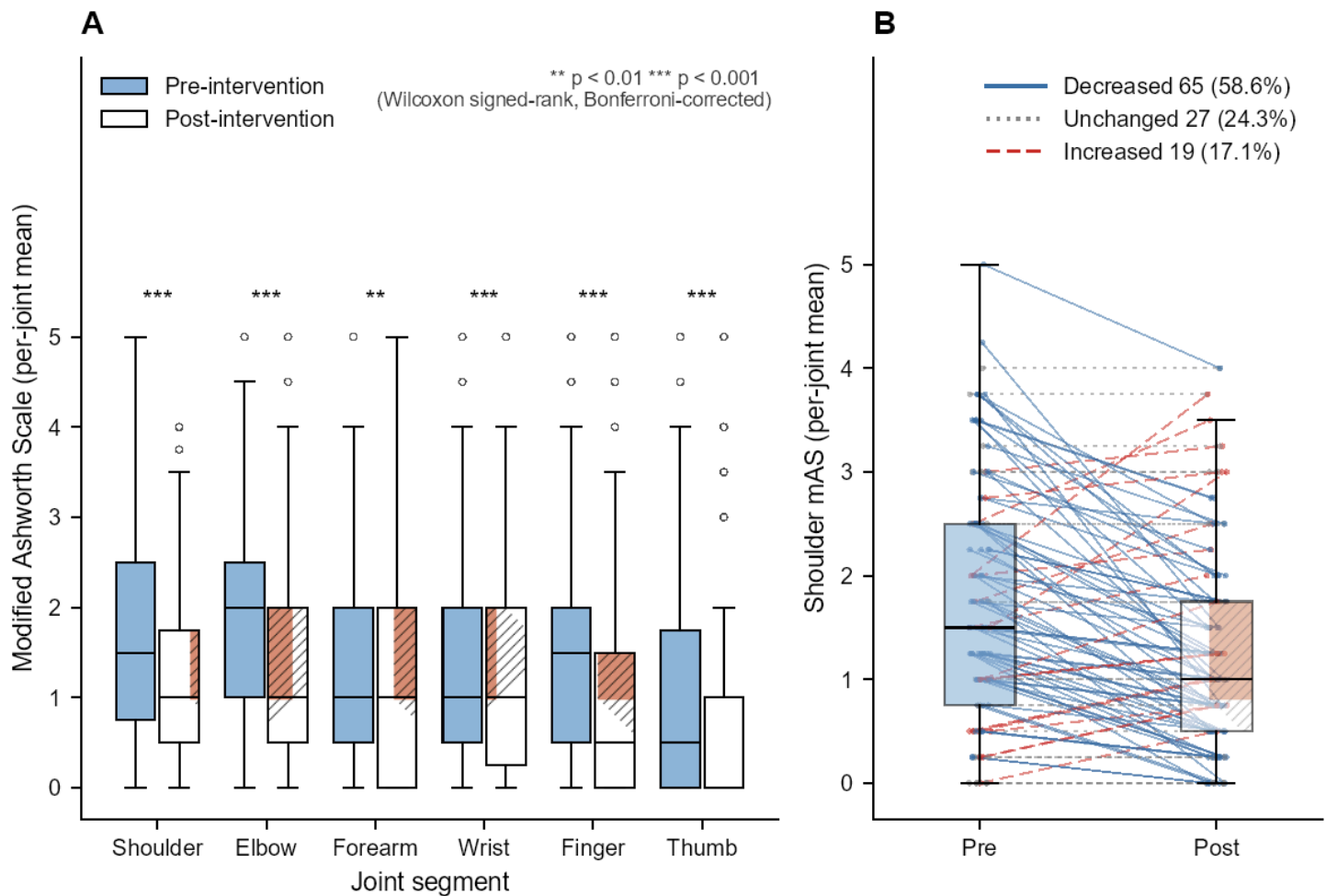


Figure 2

Modified Ashworth Scale (mAS) scores before (Pre) and after (Post) the contralesional 1 Hz rTMS program. (A) Per-joint mAS by joint segment; pre-intervention boxes blue-plain, post-intervention red-hatched. Box: median and 25th-75th percentile; whiskers: $1.5 \times$ interquartile range; dots: outliers. Asterisks denote Bonferroni-corrected Wilcoxon signed-rank results (** $p < 0.01$, *** $p < 0.001$; Table 2). (B) Individual pre-post mAS trajectories at the shoulder. Each thin line is one patient, encoded by color and line style: decreased, blue-solid, 65 (58.6 %; 95 % CI 49.3-67.3); unchanged, gray-dotted, 27 (24.3 %); increased, red-dashed, 19 (17.1 %). Lines are jittered horizontally because many patients share identical scores; vertical positions are exact. $n = 111$ at every joint.

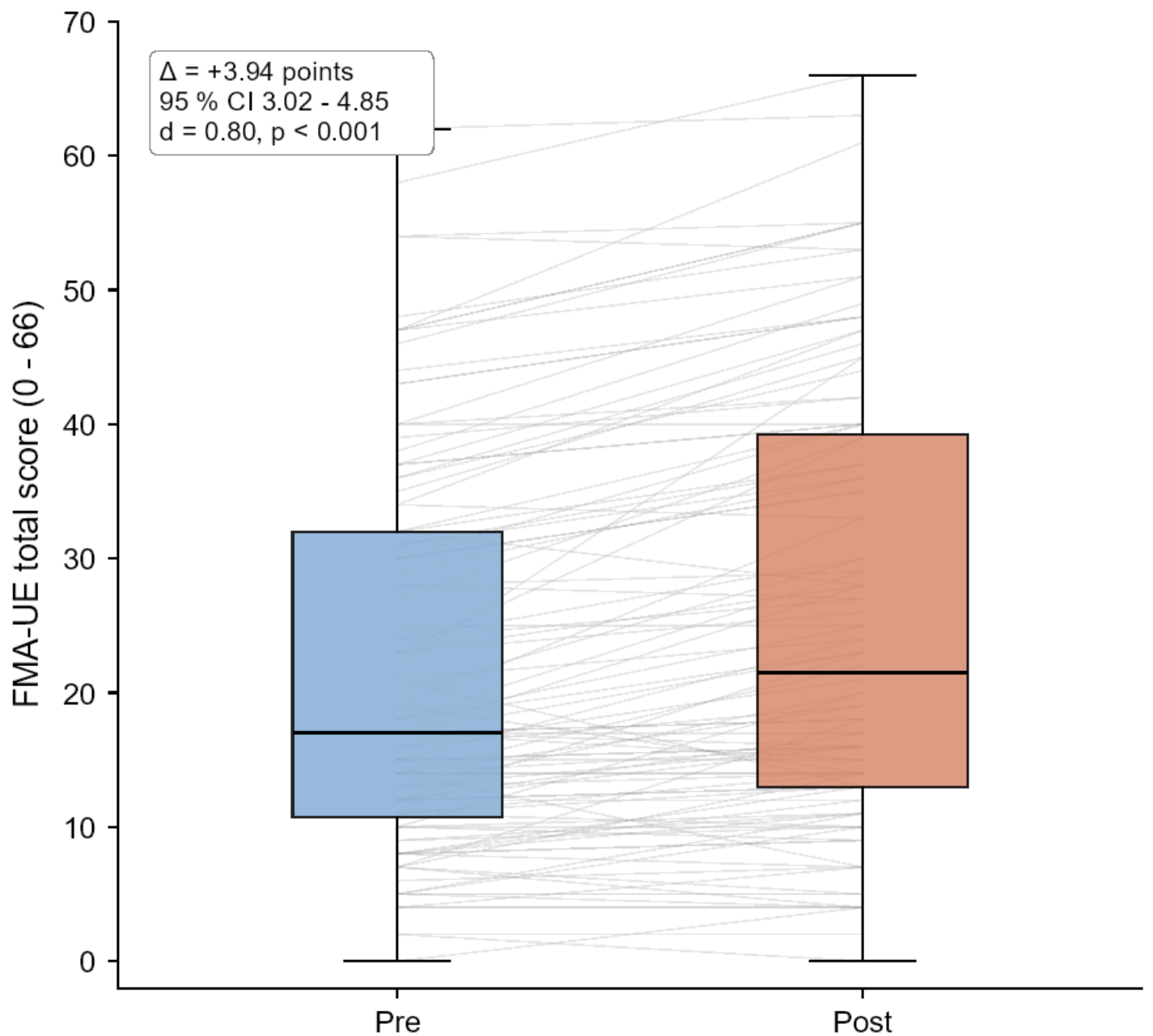


Figure 3

FMA-UE total score before and after intervention (n = 112). Box: median and IQR; whiskers: $1.5 \times$ IQR; thin gray lines: individual patient trajectories. Mean $\Delta = +3.94$ points (95 % CI 3.02-4.85), $p < 0.001$, Cohen's $d = 0.80$.

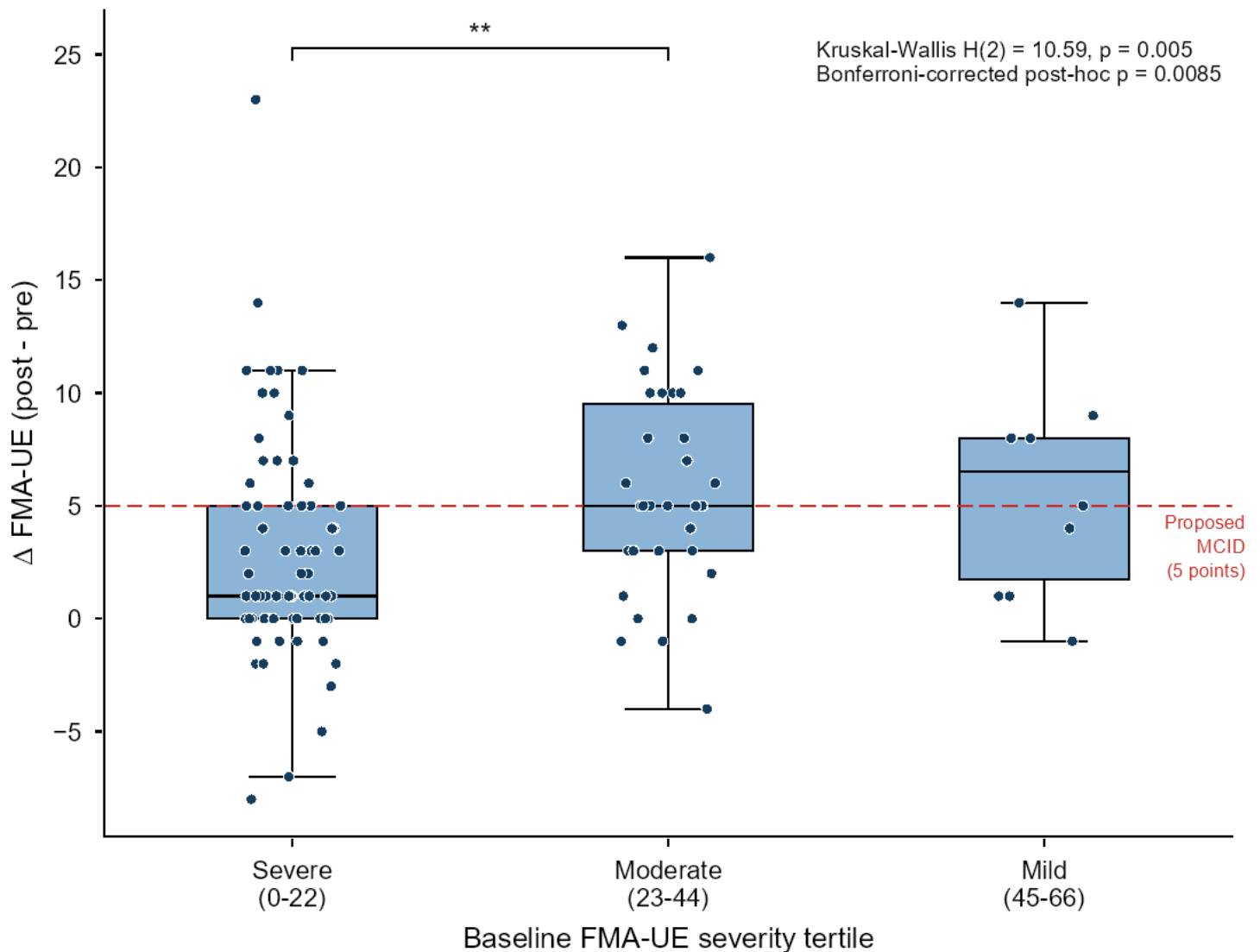


Figure 4

Distribution of Δ FMA-UE by baseline severity tertile. Boxes show median and interquartile range; whiskers extend to the most extreme values within $1.5 \times$ the interquartile range; jittered dots indicate data of individual patients. Dashed horizontal line: proposed minimal clinically important difference (MCID, 5 points; derived in mild-to-moderate chronic stroke populations (42)). The overall difference in Δ FMA-UE across tertiles was significant (Kruskal-Wallis $H(2) = 10.59$, $p = 0.005$); Bonferroni-corrected post-hoc Mann-Whitney indicates a significant difference between the severe and moderate tertiles (** $p = 0.0085$).

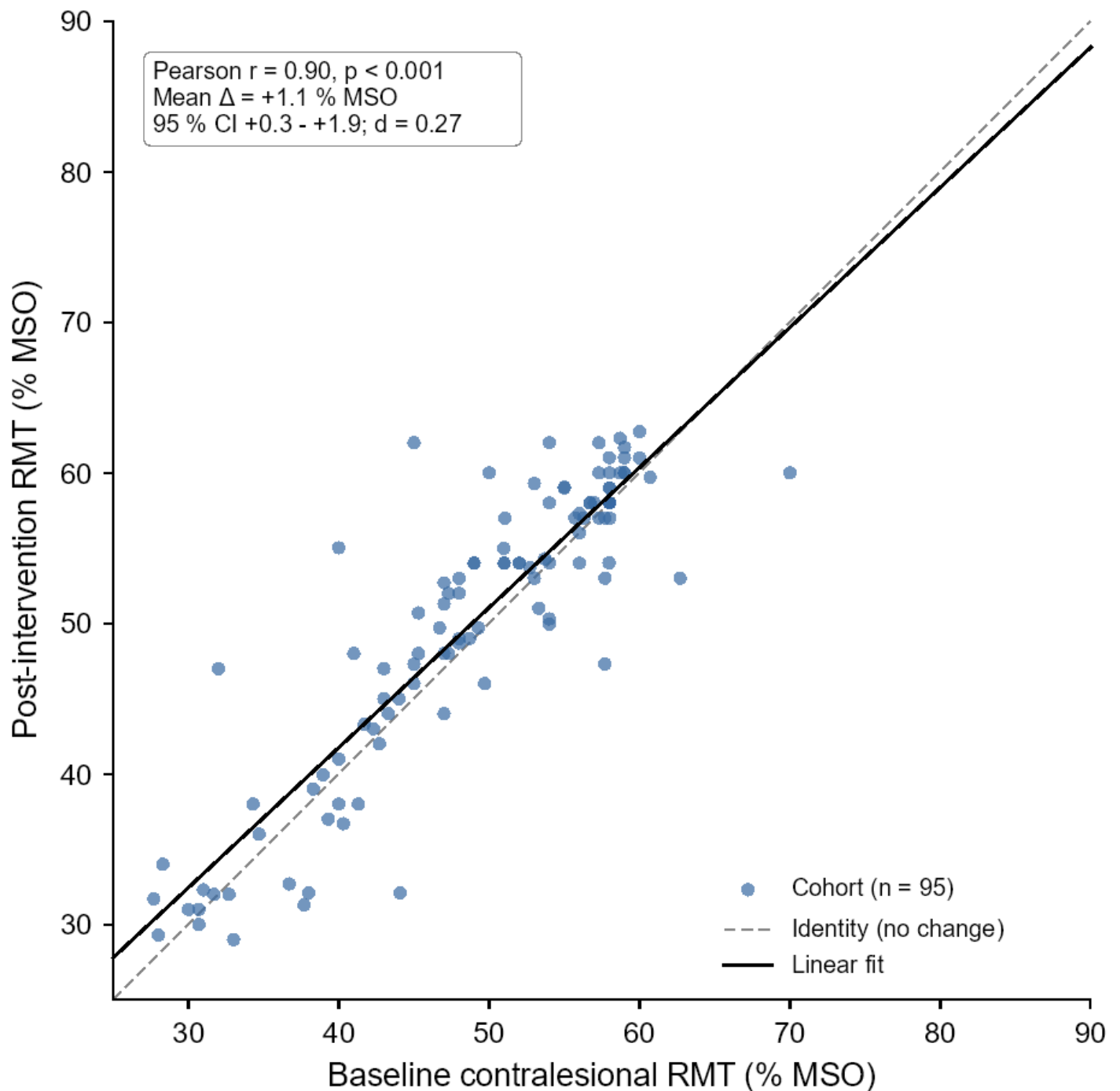


Figure 5

Within-patient relationship between baseline and post-intervention contralesional resting motor threshold (RMT). Each dot is one patient (n = 112). Dashed line: identity (no change). Solid line: fitted linear regression. Points above the identity line indicate post-intervention increase in contralesional RMT (reduced excitability). Pearson $r = 0.90$, $p < 0.001$; mean $\Delta = +1.1$ % MSO (95 % CI $+0.3$ to $+1.9$), $d = 0.27$.

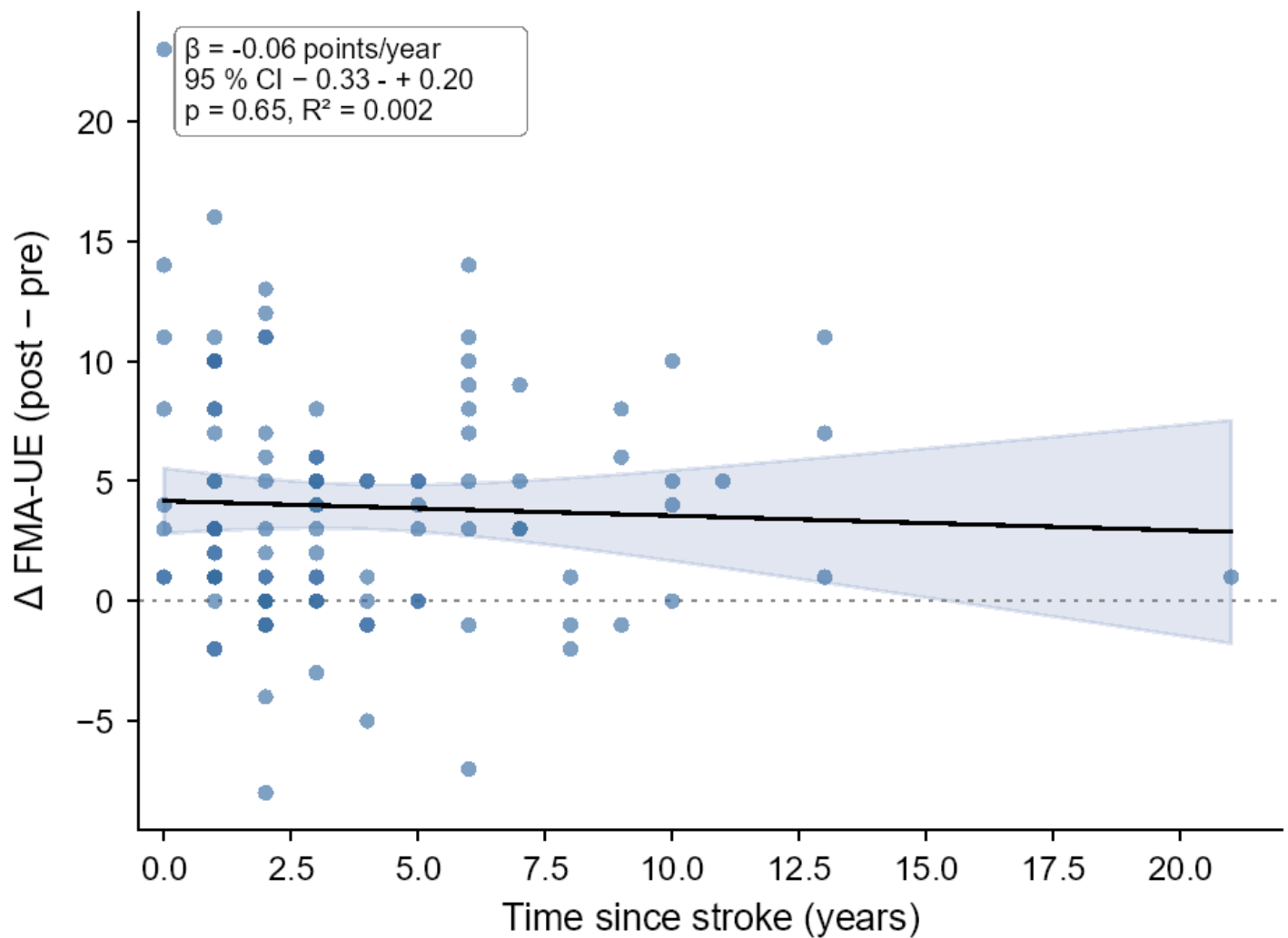


Figure 6

Relationship between time since stroke and change in FMA-UE. Solid line: fitted linear regression; shaded band: 95 % confidence interval. No significant association across the range covered by the cohort (3 months to 21 years). $\beta = -0.06$ points per year (95 % CI -0.33 to $+0.20$), $p = 0.65$, $R^2 = 0.002$.

Supplementary Files

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