PNAS Nexus, 2024, 3, pgae240
https://doi.org/10.1093/pnasnexus/pgae240
Advance access publication 9 July 2024
Research Report

Enhancing poststroke hand movement recovery: Efficacy of RehabSwift, a personalized brain–computer interface system

Sam Darvishi [a,b,*,1], Anupam Datta Gupta [c,d,1], Anne Hamilton-Bruce [e], Simon Koblar [d], Mathias Baumert [b] and Derek Abbott [b]

[a]RehabSwift Pty Ltd, 10 Pulteney Street, The University of Adelaide, Adelaide, SA 5000, Australia
[b]School of Electrical and Electronic Engineering, The University of Adelaide, Adelaide, SA 5000, Australia
[c]Department of Rehabilitation Medicine, The Queen Elizabeth Hospital, Woodville, SA 5011, Australia
[d]Adelaide Medical School, The University of Adelaide, Adelaide, SA 5000, Australia
[e]Stroke Research Programme, Basil Hetzel Institute, The Queen Elizabeth Hospital, Central Adelaide Local Health Network, Woodville, SA 5011, Australia
*To whom correspondence should be addressed: Email: sam@rehabswift.com
[1]S.D. and A.D.G. contributed equally to the work.
Edited By: Maryam Shanechi

Abstract

This study explores the efficacy of our novel and personalized brain–computer interface (BCI) therapy, in enhancing hand movement recovery among stroke survivors. Stroke often results in impaired motor function, posing significant challenges in daily activities and leading to considerable societal and economic burdens. Traditional physical and occupational therapies have shown limitations in facilitating satisfactory recovery for many patients. In response, our study investigates the potential of motor imagery–based BCIs (MI-BCIs) as an alternative intervention. In this study, MI-BCIs translate imagined hand movements into actions using a combination of scalp-recorded electrical brain activity and signal processing algorithms. Our prior research on MI-BCIs, which emphasizes the benefits of proprioceptive feedback over traditional visual feedback and the importance of customizing the delay between brain activation and passive hand movement, led to the development of RehabSwift therapy. In this study, we recruited 12 chronic-stage stroke survivors to assess the effectiveness of our solution. The primary outcome measure was the Fugl-Meyer upper extremity (FMA-UE) assessment, complemented by secondary measures including the action research arm test, reaction time, unilateral neglect, spasticity, grip and pinch strength, goal attainment scale, and FMA-UE sensation. Our findings indicate a remarkable improvement in hand movement and a clinically significant reduction in poststroke arm and hand impairment following 18 sessions of neurofeedback training. The effects persisted for at least 4 weeks posttreatment. These results underscore the potential of MI-BCIs, particularly our solution, as a prospective tool in stroke rehabilitation, offering a personalized and adaptable approach to neurofeedback training.

Keywords: brain–computer interfaces, stroke, stroke rehabilitation, neurorehabilitation, neurotechnology

Significance Statement

Stroke survivors often struggle with significant motor function impairments, affecting daily activities and imposing socioeconomic challenges. In this study, we utilized RehabSwift, a novel neurofeedback system designed for stroke rehabilitation. Compared with equivalent solutions worldwide, our solution offers a unique advantage due to its highly customizable neurofeedback protocols, which can be tailored specifically to an individual's recovery needs. This personalization is supported by our findings, which demonstrate significant improvements in motor and sensory functions among participants. Our technology, having received regulatory approval from the Therapeutic Goods Administration in Australia, is now available in commercial settings, offering a robust tool for therapists and patients alike on the challenging journey of stroke recovery.

Competing Interest: S.D. is the founder and shareholder of RehabSwift Pty Ltd, who made available a solution for the duration of the study and paid for the consumables and the salary of the personnel who assisted with the governance of the clinical trials. The other authors were not paid by RehabSwift and declared no conflict of interest.
Received: January 16, 2024. **Accepted:** June 6, 2024

Introduction

Stroke is a leading cause of long-term disability, often resulting in impaired motor functions, particularly in the hand (1–4). Despite receiving conventional therapy, almost 50% of stroke survivors experience long-term disability (5). Poststroke impairments result in substantial individual, societal, and economic burdens, according to the World Stroke Organization (6).

Traditional rehabilitation methods have shown limited success in achieving full recovery, necessitating innovative approaches (7). Brain–computer interface (BCI) technology has emerged as a promising avenue for enhancing hand function after stroke (8–17).

Motor imagery–based BCIs (MI-BCIs) translate a user's imagined hand movements into actual actions on a screen or via a robotic hand, using a combination of electrical brain activity recorded from the scalp and signal processing algorithms. While there is promising evidence regarding the potential benefits of MI-BCIs for poststroke movement recovery (18–20), further research is needed to establish their reliability and efficacy as a standard therapeutic approach (21, 22).

Our previous work has highlighted the advantages of proprioceptive feedback over traditional visual feedback (23) and underscored the critical role of customizing the delay between brain activation and passive hand movement (24). Building on these positive findings, we achieved significant improvement in hand movement in a stroke patient after just 10 therapy sessions (25). Leveraging these prior results, we developed a novel BCI system that customizes the optimal site (channel), the spectral frequency within the beta band (16–30 Hz), and the frequency of feedback received during motor imagery (MI) performance.

The present study aims to assess the effectiveness of our innovative BCI therapy, in a cohort of chronic stroke survivors for hand movement recovery. We hypothesized that 18 sessions of our personalized neurofeedback training would lead to a clinically significant reduction in poststroke arm and hand impairment, with effects persisting for at least 4 weeks.

Results

Our study recruited chronic stroke survivors from South Australia during 2020–2021, focusing on individuals with stable poststroke conditions and impaired motor capabilities specifically of the hand. Participants underwent personalized neurofeedback training, which targeted specific electroencephalogram (EEG) channels and frequency bands tailored to their neurophysiological profiles. Training sessions were conducted three times weekly over 6 weeks, using a customized EEG cap and feedback system to engage MI and relaxation phases, which were adjusted based on the individual's performance and reaction times. Outcome measures, including motor function and sensory feedback performance, were assessed at baseline, immediately postintervention, and during a 4- to 6-week follow-up to evaluate the lasting impacts of the training. A more detailed explanation of the study design may be seen in the Materials and Methods section.

Participants

For this study, we screened 25 prospective participants to obtain a sample of 12 stroke patients; 13 candidates did not meet the inclusion/exclusion criteria. Table 1 summarizes the attributes of the 12 participants included in the trial.

Performance measures

Behavioral changes were monitored using Fugl-Meyer upper extremity (FMA-UE (26)) motor assessment as the primary outcome measure. We also used the action research arm test (ARAT) (27), the reaction time of the affected and intact hands, unilateral neglect (28), spasticity (29), grip and pinch strength of the affected hand, goal attainment scale (GAS) (30), and FMA-UE sensation (26) as the seconday outcome measures. Note that the last four secondary tests were added after the first cohort of participants underwent the study and reported gaining outcomes in their sensory functions and hand strength. As a result, we added FMA-UE sensation, grip strength, pinch strength, and GAS tools. Therefore, for these four tests, the sample size was smaller than 12. For details of the tests, see the Supplementary Information.

The results of the study are demonstrated in Fig. 1, and Table 2 summarizes reports of the outcome measures, the sample size, the average value measured at pre- and posttraining and follow-up sessions, and the P-values of the statistical analysis. Considering the categorical nature of the scales, no average was calculated for the GAS. Also, reaction time measurement (RTM) came into the picture only during the 18 training sessions, and no measurement of reaction time was recorded during the follow-up session.

Primary outcome

BCI neurofeedback significantly improved FMA-UE motor scores at posttraining (45.08) and follow-up (46.17) compared with baseline (36.75) measurement ($F(1.352, 14.87) = 20.02$, $P = 0.0002$). The

Table 1. Study participants' characteristics.

Participants	Age (year)	Gender	Type of stroke	Time poststroke	Affected body side	Handedness
P1	76	M	Ischemic	9 years	Left	Right
P2	68	M	Hemorrhagic	6 years	Left	Right
P3	57	F	Hemorrhagic	6 years	Right	Right
P4	51	F	Ischemic	9 months	Right	Left
P5	75	M	Ischemic	1.5 years	Left	Left
P6	59	F	Hemorrhagic	9 years	Right	Right
P7	54	M	Hemorrhagic	2 years	Right	Right
P8	72	M	Hemorrhagic	2 years	Right	Left
P9	68	M	Ischemic	2 years	Left	Right
P10	37	F	Hemorrhagic	6.5 years	Left	Right
P11	31	F	Hemorrhagic	1 year	Right	Right
P12	59	F	Hemorrhagic	41 years	Left	Right
Median/ summary	59	6 males 6 females	4 ischemic 8 hemorrhagic	4 years	6 left 6 right	3 left 9 right

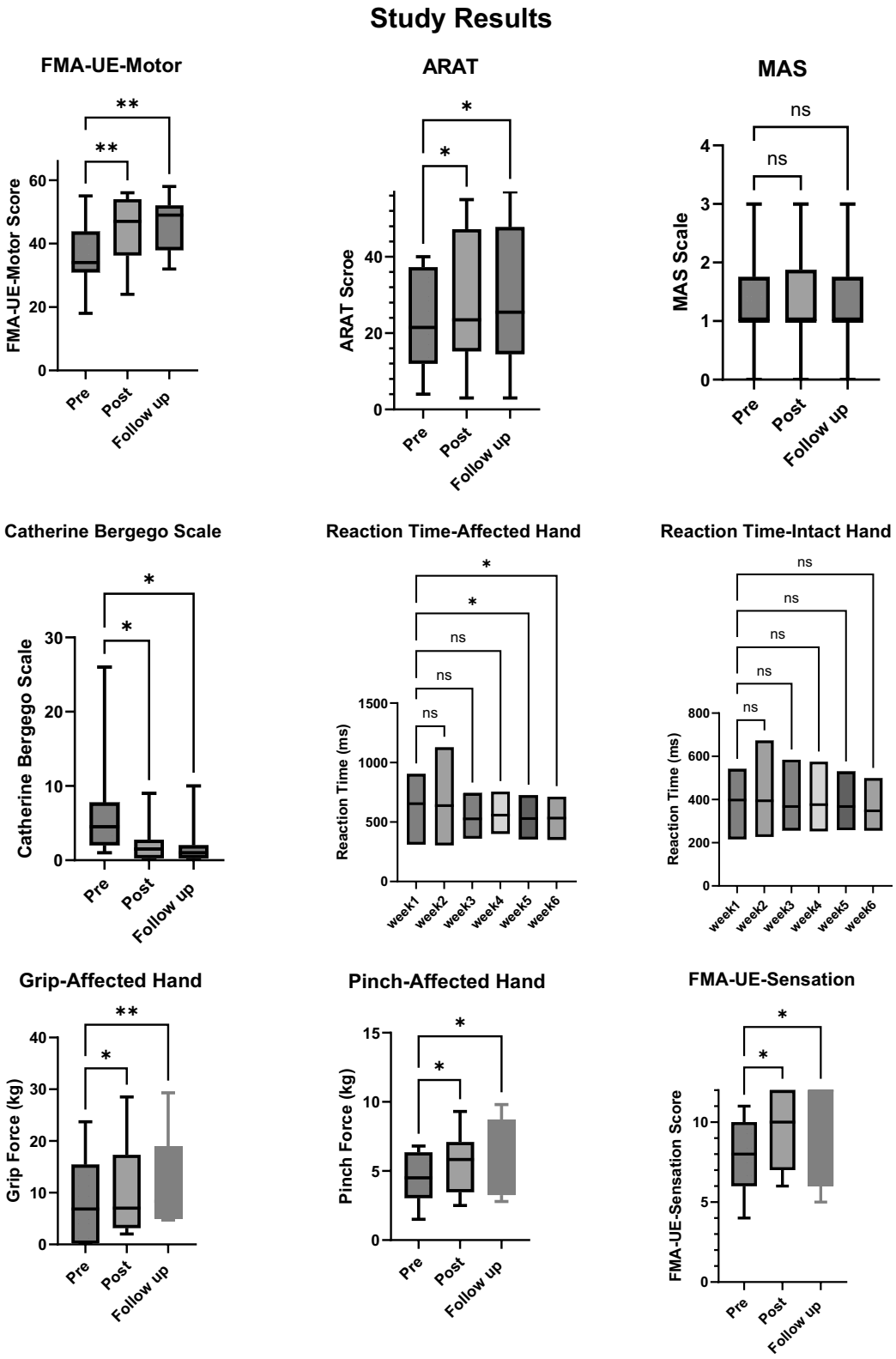

Fig. 1. Participant assessment outcomes before, after, and 4–6 weeks after completing biofeedback training. The upper and lower sides of the boxes show 25 and 75% quartiles, and the whiskers depict the minimum and maximum of the data. The mean value for the normally distributed data is the horizontal line drawn between the 25 and the 75% quartiles. The asterisk and two asterisks denotes statistically significant differences with *P*-value <0.05 and *P*-value <0.01, respectively. ns: nonsignificant differences; MAS, Modified Ashworth Scale.

post hoc t test confirmed significant improvements at both posttraining ($t(11) = 4.771$, $P = 0.0012$) and follow-up ($t(11) = 4.704$, $P = 0.0013$), suggesting that neurofeedback training improved upper limb movement and lasted over a month. As listed in Table 3, the level of improvement was clinically significant for 9 of 12 participants (75%).

Table 2. Summary of average values for outcome measures and their corresponding *P*-values.

Outcome measure	Primary or secondary	Sample size	Pre	Post	Follow-up	*P*-values
FMA-UE motor (66)	Primary	12	36.75	45.08	46.17	**0.0002**
ARAT (57)	Secondary	12	22.75	28.08	29.17	**0.0086**
Modified Ashworth (0–4)	Secondary	12	1.16	1.25	1.25	0.8187
Neglect (30)	Secondary	12	6.88	2.25	2.13	**0.0014**
Reaction time affected (ms)	Secondary	12	654	541	N/A	**0.0359**
Reaction time intact (ms)	Secondary	12	396	353	N/A	0.1464
Grip (kg)	Secondary	8	8.22	10.73	12.18	**0.0032**
Pinch (kg)	Secondary	8	4.46	5.57	6.03	**0.0161**
FMA-UE sensation (12)	Secondary	7	7.57	9.71	9.28	**0.0041**
Goal attainment score (–2 to +2)	Secondary	10	N/A	N/A	N/A	N/A

The *P*-values for outcome measures that revealed statistically significant differences are shown in bold. N/A, not applicable.

Table 3. Individual FMA-UE assessment test results measured before and after the neurofeedback training and at the follow-up session 4–6 weeks after finishing the program.

Subjects	FMA-UE motor			Pre- vs. postimprovement	Clinically significant?
	Pre	Post	Follow-up		
P1	31	37	38	6	Yes
P2	34	47	47	13	Yes
P3	29	36	38	7	Yes
P4	34	54	52	20	Yes
P5	40	54	58	14	Yes
P6	18	24	33	6	Yes
P7	52	52	52	0	No
P8	45	55	52	10	Yes
P9	31	33	32	2	No
P10	55	56	54	1	No
P11	39	46	48	7	Yes
P12	33	47	50	14	Yes
Average	36.75	45.08	46.17	8.33	9 yes/3 no

Secondary outcomes

BCI neurofeedback training also significantly improved the ARAT scores from 22.75 at baseline to 28.08 and 29.17 at posttraining and follow-up ($F(1.738, 19.11) = 6.569$, $P = 0.0086$). The post hoc t test indicated significant improvements at both posttraining ($t(11) = 3.218$, $P = 0.0151$) and follow-up ($t(11) = 2.876$, $P = 0.0274$).

The Friedman test of the Modified Ashworth Scale showed no significant change in muscle stiffness in the arms ($\chi^2(2) = 0.400$, $P = 0.8187$). In contrast, the Catherine Bergego scores improved from pretraining (6.88) to posttraining (2.25) and at follow-up (2.13) measurement (Friedman test: $\chi^2(2) = 12.78$, $P = 0.0014$), suggesting significantly fewer neglect symptoms. The post hoc Dunn's z test indicated significant improvements at both posttraining ($z = 2.625$, $P = 0.0173$) and follow-up ($z = 2.625$, $P = 0.0173$).

Neurofeedback training also significantly reduced the reaction time for the affected hand across the weeks, demonstrating that training enhanced the integration of sensory and motor functions ($F(1.941, 21.35) = 3.945$, $P = 0.0359$). Week 1: 654 ms; week 6: 541 ms. The post hoc t test indicated significant improvements for week 5 ($t(11) = 3.699$, $P = 0.0174$) and week 6 ($t(11) = 3.419$, $P = 0.0283$). In contrast, neurofeedback training had no significant effect on the intact hand's reaction time (week 1: 396 ms vs. week 6: 353 ms; $F(2.867, 31.54) = 1.934$, $P = 0.1464$).

The grip strength of the affected hand improved throughout training from 8.22 kg at baseline to 10.73 and 12.18 kg at posttraining and follow-up, respectively ($F(1.316, 9.213) = 13.75$, $P = 0.0032$). The post hoc t test indicated significant improvements at both posttraining ($t(7) = 2.565$, $P = 0.0373$) and follow-up ($t(7) = 5.264$, $P = 0.0023$) compared with the baseline.

The 3-point pinch strength of the affected hand, which is important for daily tasks, significantly increased throughout the study by about 26% (pretraining: 4.46 kg; posttraining: 5.57 kg; follow-up: 6.03 kg; $F(1.301, 9.110) = 7.836$, $P = 0.0161$). The post hoc t test indicated significant improvements at both posttraining ($t(7) = 2.872$, $P = 0.0473$) and follow-up ($t(7) = 2.971$, $P = 0.0411$).

The Friedman test of FMA-UE sensation revealed significant differences between measurements (pretraining: 7.57 vs. posttraining: 9.71 vs. follow-up: 9.28; $\chi^2(2) = 10.80$, $P = 0.0041$). Post hoc Dunn's z test indicated significant improvements at posttraining ($z = 2.405$, $P = 0.0323$) that were still present at follow-up ($z = 2.405$, $P = 0.0323$) compared with the baseline.

Considering the subjective nature of the GAS, we used a qualitative approach rather than statistical analysis. Participants had various levels of success in achieving their personal goals through the training, with 60% meeting or even exceeding their expectations. Out of 10 participants who reported their level of goal achievement, 40% reached their goals somewhat less than expected, 40% met expectations, and 20% exceeded expectations.

The effect sizes

Figure 2 illustrates the calculated effect sizes for the outcomes following neurofeedback training. Specifically, for grip, pinch, and the ARAT, we observed small effect sizes ranging from 0.2 to 0.5. In contrast, medium effect sizes, between 0.5 and 0.8, were noted for reaction time (affected hand), neglect, FMA-UE motor, and FMA-UE sensation. These effect sizes provide a quantitative measure of the intervention's impact across various functional domains.

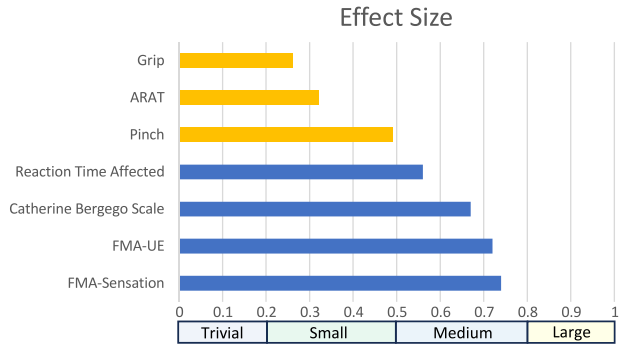

Fig. 2. Demonstrating the effect sizes of the neurofeedback training. For grip, pinch, and ARAT, we observed small effect sizes (0.2–0.5) and for reaction time, neglect, FMA-UE motor, and FMA sensation, there were medium effect sizes (0.5–0.8).

Discussion

Stroke often results in debilitating motor impairments, the most common being upper limb involvement (31), which impact an individual's quality of life and independence. Despite completing conventional therapies, a significant number of stroke survivors face ongoing difficulties in regaining full motor function. This study sought to address this challenge by investigating the effectiveness of our personalized BCI therapy in facilitating hand movement recovery among chronic stroke survivors.

Our findings support the hypothesis that 18 sessions of personalized neurofeedback training can lead to a clinically significant reduction in poststroke arm and hand impairment, with effects persisting for at least 4 weeks. The primary outcome measure, the FMA-UE assessment, demonstrated a substantial improvement in reducing motor impairment. This is a noteworthy achievement, as the FMA-UE assessment is widely regarded as a gold standard for evaluating upper extremity motor function following stroke (22). The observed improvements surpass the threshold for minimal clinically significant difference (32), for 75% of the participants, emphasizing the practical relevance of our findings (32).

Moreover, the secondary outcome measures further support the positive impact of our solution. The ARAT, which assesses upper limb function through various functional tasks, exhibited significant improvements. These improvements exceeded the clinically significant threshold (33), indicating meaningful changes in patients' ability to perform daily activities. Grip and pinch strength assessments, crucial for activities of daily living, both demonstrated substantial increases, further underscoring the potential of the studied solution to enhance functional outcomes.

Our study also considered RTMs for the affected and intact hands, because reaction times in acute stroke patients are associated with longer term cognitive outcomes (34, 35). Information processing speed manifested by reaction time significantly correlates to functional outcomes over and above age, depression, and the Barthel index (36). Administering transcranial magnetic stimulation to the motor cortex of the lesioned hemisphere resulted in reaction time delays in the contralateral paretic hand correlated well with functional recovery, which reflects the correlation between reaction time of the paretic hand and the level of recovery (37). Our results revealed a significant reduction in reaction time for the affected hand, highlighting enhanced processing of sensory information and motor execution. This outcome holds particular importance, as it suggests that personalized neurofeedback training not only aids in motor recovery but also enhances the efficiency of sensory-motor integration—an aspect often compromised following stroke. The patterns of sensory and motor recovery after stroke are not the same but interrelate, and the sensory deficit level may affect motor recovery (38).

The Modified Ashworth Scale, used to assess muscle spasticity, did not yield significant differences across time points. This could suggest that our method primarily influences motor function rather than directly impacting muscle tone.

A recent study by Bassolino et al. (39) highlights significant distortions in body and peripersonal space representations among chronic stroke patients. They also found that such misrepresentations are often exacerbated by lesions in regions such as the superior frontal gyrus and parietal operculum (39). These findings underscore the complexity of neural recovery and the necessity for tailored rehabilitation approaches. Our system addresses these challenges by integrating targeted neurofeedback and proprioceptive feedback, aiming to rectify the impaired sensorymotor integration and enhance limb and space perception. This approach suggests potential improvements in how peripersonal space and body dimensions are perceived and interacted with, thereby enhancing overall rehabilitation outcomes.

Furthermore, the altered feelings of embodiment and agency reported by Bassolino et al. emphasize the importance of these factors in patients' adaptation to life poststroke. Our incorporation of real-time proprioceptive feedback is particularly relevant here, as it seeks to restore a sense of agency and ownership over affected limbs. By fostering a more accurate body representation and enhancing the feeling of embodiment, our system may influence the physical and psychological recovery processes. The results showed improvements on the Catherine Bergego scale. The observed improvements may be related to addressing the intricate dynamics of body representation, personal agency, and enhanced perceptual-cognitive mechanisms through personalized neurofeedback.

The GAS provided qualitative insights into patients' perceived achievements. While not quantitatively examined, it is worth noting that a substantial portion of participants reported reaching their set goals, with some even exceeding their expectations. These self-reported achievements highlight the subjectively perceived value of this novel approach in facilitating personal goal attainment during the rehabilitation process.

The analysis of effect sizes for the neurofeedback training outcomes offers insightful observations. The primary measure, the FMA-UE motor, along with three secondary measures, demonstrated medium effect sizes, indicative of a moderate impact of the intervention. Meanwhile, the remaining secondary measures exhibited small effect sizes. Crucially, all evaluated outcome measures presented nontrivial effect sizes, suggesting that the neurofeedback training exerted a measurable and meaningful influence across different aspects of motor and sensory recovery.

Comparing our findings with previous research, several parallels and distinctions emerge. Similar to prior studies (8–11, 15, 20), our results confirm the beneficial effects of neurofeedback training on motor recovery poststroke. Particularly, our findings regarding the enhancement of motor function mirror those reported in previous studies (11, 40, 41). However, our study extends those findings by demonstrating that customized neurofeedback training, which tailors feedback update intervals (FUIs) and modalities to individual patients' neurophysiological profiles, can lead to significant improvements in areas like sensory feedback and neglect, which have been less extensively covered in earlier studies.

Notably, while the use of Laplacian configurations and EEG signal processing techniques, such as event-related desynchronization

(ERD), in our solution is well-established in the field, our approach differentiates itself through the integration of these techniques into a real-time, adaptive neurofeedback system. Unlike many conventional systems that utilize fixed settings for all users, our system customizes the detection of ERD tailored to the individual's affected brain areas, adjusts in real-time based on ongoing session feedback and through progressive tune-up of the FUIs according to the user's performance in prior sessions. This adaptive approach is an innovative departure from more static methods typically used in clinical settings. Our strategy allows for more precise and effective modulation of neurofeedback, potentially increasing the therapeutic outcomes of the training.

The mechanisms underlying our solution's effectiveness likely involve the combination of personalized neurofeedback training—where the optimal electrode and the frequency within the beta band were selected—and real-time proprioceptive feedback with the optimal FUI. Our previous research emphasized the advantage of proprioceptive feedback over traditional visual feedback (23). Proprioceptive feedback is crucial in reestablishing sensorimotor integration, enabling patients to better connect their mental intentions to physical movements.

Additionally, customizing the delay between brain activation and passive hand movement (24, 25) is another key feature of our personalized neurofeedback solution. This customization allows for a personalized and adaptive training experience, ensuring the therapy aligns with each patient's unique needs and capabilities. This adaptability likely contributes to the observed improvements, as it tailors the training to the individual's current state of recovery.

In addition to its scientific efficacy, our system holds substantial promise from an industrial and commercial perspective. The development of this technology represents a significant advancement in neurofeedback technologies for stroke rehabilitation, with several key factors including: (i) validation of the market demand for novel stroke rehabilitation solutions; (ii) fostering collaboration between the industry and academia on goal-oriented collaborative research in neurotechnology; and (iii) commercial availability of the solution following the approval by Therapeutic Goods Administration in Australia.

In considering the accessibility of our system, it is important to acknowledge that it is designed primarily for clinical use rather than for at-home therapy. This distinction stems from several factors that affect its practical deployment outside of professional healthcare settings, including cost-effectiveness, size and portability, and the advantages of the clinical settings in delivering the service. Consequently, while this solution demonstrates substantial potential in enhancing stroke rehabilitation outcomes, its current implementation is best suited for use in clinical settings. Future developments may focus on reducing the cost and size to make such technologies more accessible for home use.

Limitations and future directions

Despite the promising results, this study has several limitations. First, the sample size was relatively small, which may limit the generalizability of our findings. Future research should involve larger cohorts to further validate the efficacy of our proposed method. Additionally, the absence of a control group restricts our ability to attribute the observed improvements solely to the studied technology. Another potential confounder could be concurrent conventional therapy at home. A randomized controlled trial would provide stronger evidence of the therapy's effectiveness.

We also acknowledge issues regarding the repeatability of neurofeedback training sessions and the cross-subject variability in experience, engagement, and understanding. We recognize these as intrinsic challenges within neurofeedback training and propose future research on the development of methods to further reduce session variability and adaptation of training to individual variability in engagement and cognitive capacity.

Furthermore, the follow-up period was limited to 4 to 6 weeks after the completion of training sessions. Extending the follow-up period to assess the longevity of the observed improvements would enhance the understanding of our system's long-term effects. Future investigations could study the effects of a more intensive neurofeedback training program on recovery outcomes, particularly concerning the number of sessions and the program duration.

Materials and methods

We recruited South Australian chronic stroke survivors from the community between 2020 and 2021. Patients were included if they (i) were at least 6 months poststroke and in a stable condition; (ii) had impaired motor capabilities in their affected arm determined by an ARAT score of <45 out of 57; (iii) had intact cognitive functions determined by the mini-mental state examination score to be >26 out of 30; (iv) were independently mobile—with or without a walking aid; (v) had no excessive tone in their arm and hand muscles determined by the Modified Ashworth test score to be <3 out of 4; (vi) could perform vivid MI—by screening their ability to generate discriminable MI vs. rest EEG signals; (vii) had an (almost) intact sense of proprioception—by screening their blind judgment of comparing the size of seven polystyrene balls (42) with >50% accuracy; and (viii) fully understood and comprehended auditory instructions in plain English to perform MI.

Study candidates were excluded if they (i) had comorbidities such as arthritis in the hands/fingers of their affected side that could interfere with the neurofeedback training, (ii) could not fulfill the visit attendance requirements, or (iii) had significant visual or hearing impairment that impeded their ability in receiving auditory and/or visual instructions.

Study design

In this study, we investigated: (i) whether personalized neurofeedback training—where factors such as selected electrodes, frequency bands, and the FUI were adjusted according to individuals' biometric attributes—impacts the recovery of arm and hand functions following stroke and (ii) whether the effects of this customization on the recovery outcomes persist for at least 4 weeks after finishing the program. Therefore, the assessments were implemented before intervention, postintervention and during 4–6 weeks postintervention. The tests were implemented for each participant in the assessment weeks (weeks 1 and 8). In the intervention weeks (weeks 2–7), BCI training sessions were conducted on Monday, Wednesday, and Friday. Then, in the follow-up weeks, performance indices were measured again within 4 to 6 weeks after their last neurofeedback training session to investigate how long potential changes lasted. Note that the study participants were not admitted to hospitals and lived in their homes and bringing them back to the laboratory for the follow-up test precisely 4 weeks after finishing the trials was not practical. Therefore, we set a 3-week window (4–6 weeks after the trials) to be able to record the follow-up measurements for the participants. The design schedule is presented in Table 4.

Table 4. Schedule of the BCI training and RTM.

	Monday	Tuesday	Wednesday	Thursday	Friday
Week 1	Pretraining assessments				
Week 2	RTM + BCI	—	RTM + BCI	—	RTM + BCI
Week 3	RTM + BCI	—	RTM + BCI	—	RTM + BCI
Week 4	RTM + BCI	—	RTM + BCI	—	RTM + BCI
Week 5	RTM + BCI	—	RTM + BCI	—	RTM + BCI
Week 6	RTM + BCI	—	RTM + BCI	—	RTM + BCI
Week 7	RTM + BCI	—	RTM + BCI	—	RTM + BCI
Week 8	Posttraining assessments				
Weeks 11–13	Follow-up assessments				

The study conformed to principles outlined in the Declaration of Helsinki and was approved by the local human ethics committee of the University of Adelaide and the Central Adelaide Local Health Network. All participants gave written informed consent to participate in the study, and all data were de-identified.

Neurofeedback training setup

We used a 21-channel Mitsar EEG amplifier, containing 21 unipolar and four bipolar channels and a custom-built 11-channel EEG cap (Medical Computer Systems) that covered the sensorimotor cortex of the ipsilesional brain was used for data acquisition. The 11 channels in the left-sided cap that were used for those with right-hand hemiparesis included F_3, FC_5, FC_3, FC_1, C_5, C_3, C_1, CP_5, CP_3, CP_1, and P_3 channels. The right-sided cap used for those with left-hand hemiparesis, included F_4, FC_2, FC_4, FC_6, C_2, C_4, C_6, CP_2, CP_4, CP_6, and P_4 channels. According to the participants' screening session results, a selected channel and a small Laplacian configuration of EEG channels centered around it, and its optimum frequency within 16–30 Hz were chosen for the training session. The selected channel was one of the three central channels that, depending on the affected side, were $FC_{3/4}$, $C_{3/4}$, and $CP_{3/4}$. The optimum frequency of the selected channel for each participant was the 2-Hz frequency bin within 16–30 Hz, which maximized the difference in the average spectral power for the MI vs. relaxation trials recorded during the screening session. Further details of the channels and frequency bin selection of the screening session may be seen in our prior study (25). To cope with the real-time constraints of the BCI system with very short FUIs, only five EEG channels (one central and four neighboring channels) were used to record EEG signals during training sessions. The AF_z and FC_z channels were used as the ground and reference channels, respectively. The impedance between the scalp and recording electrodes was kept below 20 kΩ. The sampling frequency was set to 250 Hz. A band-pass filter with corner frequencies set to 0.1 and 48 Hz and a 50-Hz notch filter were applied to remove the direct current (DC) offset and nonrelated high-frequency elements.

Our system uses proprietary software (IntelliTime, RehabSwift Pty Ltd, Adelaide, South Australia) that includes three modules for RTM, screening, and neurofeedback training and was used for screening, measuring reaction times, and running the neurofeedback training sessions.

To provide proprioceptive feedback, we used a pair of orthoses (one for each hand) designed and developed by RehabSwift Pty Ltd to passively extend four fingers (Pro-Rehab, RehabSwift Pty Ltd). One orthosis was associated with the participant's MI of their affected hand to provide proprioceptive feedback during MI. The other orthosis, which was not involved with the patient's hand, provided visual feedback via observation of the orthosis extension during relaxation trials. The angle of the orthosis was controlled via a servomotor, which received commands from a servo controller module. The servo controller module was operated by IntelliTime, and the servomotors were operated accordingly. Figure 3 illustrates the setup for the BCI training session.

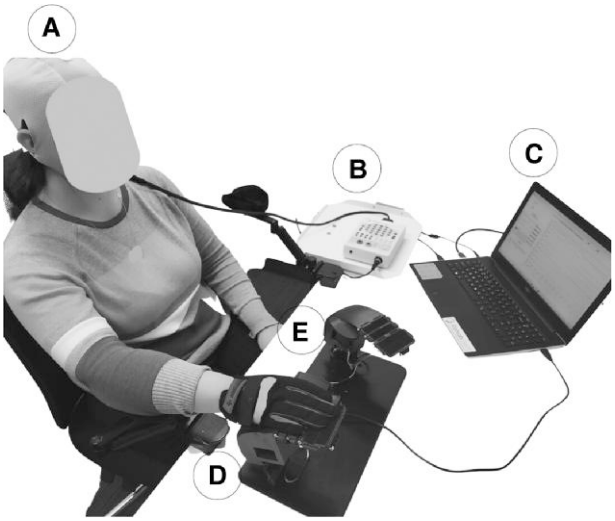

Fig. 3. A setup of the neurofeedback training sessions for a typical participant whose right side is affected by stroke. (a) The EEG cap records EEG signals. (b) The EEG amplifier receives and amplifies the EEG signals and then sends them to a laptop PC for processing. (c) The PC processes the EEG signals and accordingly commands the orthoses. (d) The right orthosis provides proprioceptive feedback during MI. (e) The free-running left orthosis provides visual feedback during relaxation. Note that for participants with an affected left side, their left hand would be engaged with the left orthosis instead. PC, personal computer.

Time course of training sessions

Each training session included 8 runs, comprising 20 trials with 10 MI of finger extension of the affected hand and 10 relaxation trials, ordered randomly. Each trial started with an auditory command at $t = 0$ s, followed by another auditory cue at $t = 3$ s. It instructed the patient to perform relaxation or MI of their affected hands' finger extension. After 1 s of MI/relaxation performance, feedback provision started and was updated at every predetermined FUI value for each session (see below). At $t = 7$ s, the trial finished, and after a 2- to 4-s intertrial interval, the subsequent trial started. Figure 4 illustrates the time course of neurofeedback training sessions.

The FUI calculation

We aimed to investigate whether personalized neurofeedback training, by customization of factors such as the target site for neurofeedback, frequency bands, and the adjustment of FUI, impacts the recovery of arm and hand motor functions after stroke. Our system's proprietary algorithm adapts the FUI throughout the neurofeedback sessions. This algorithm is designed to optimize reinforcement and Hebbian learning in a structured manner, with initial and final FUI values determined by the reaction times of both the intact and affected sides.

Importantly, the reaction time of the affected side establishes the FUI for the initial session, which could be as long as 1,500 ms. In subsequent sessions, the FUI is adjusted, considering various factors, such as BCI performance accuracy in previous sessions, the history of reaction times, and the measured reaction time on the training day. Readers can refer to RehabSwift's filed patent (43).

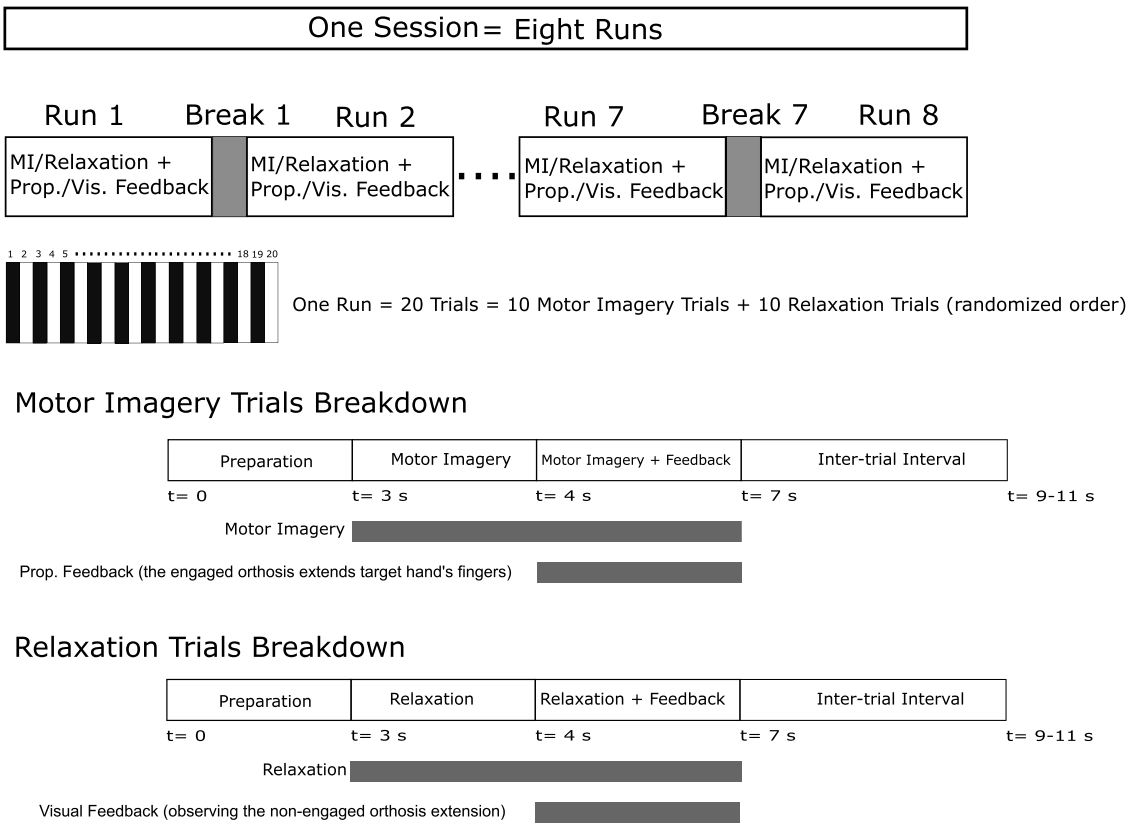

Fig. 4. An illustration of the time course of each neurofeedback training session. Each session encompasses 8 runs, and each run includes 20 trials. Each trial starts with a ready preparation cue at $t = 0$ s, followed by another command right/left/relax at $t = 3$ s that guides the participant to perform relaxation or MI of their affected side finger extension. After 1 s of MI/relaxation performance, feedback provision starts and updates recurrently according to each session's FUI value. At $t = 7$ s, the trial finishes, and after an intertrial interval of 2–4 s ($t = 9$–11 s), the subsequent trial starts. Prop, proprioceptive; Vis, visual.

Signal processing

The IntelliTime software employs an autoregressive (AR) model for the detection of ERD (44), which is a measure commonly used to detect changes in brain state during MI tasks. This approach allows for the detection of spectral power decreases in the beta frequency band (16–30 Hz), indicative of increased cortical activity. Compared with Fourier-based methods, the AR model provides enhanced temporal resolution, which is critical in real-time neurofeedback systems.

The maximum entropy method (45) was utilized to establish the AR model for the EEG data. Employing a 16th-order AR model, our system estimated the spectral power for the most recent 500 ms. The estimated power was calculated at subject-specific frequencies within the selected 2-Hz frequency bin of the beta band and electrode positions identified during the screening session. To reduce false positives in the classifier, it implemented the following normalization process: (i) spectral power data from the last 18 s of both imagery and relaxation trials (equally represented) were buffered and continuously updated; (ii) the average and SD of this buffered data were calculated; (iii) each spectral power measurement derived from the AR model was normalized by subtracting the buffer's average and then dividing by the buffer's SD; (iv) a negative normalized spectral power indicated ERD, while positive values suggested relaxation. After each FUI, the target orthosis incrementally extended the affected hand's four fingers, if an ERD was detected. For relaxation trials, however, the absence of ERD incrementally extended the other orthosis and provided relaxation trials with visual feedback through observation of the orthosis extension. The total extension/flexion range of the orthosis was 90°, and the extension angle of the orthoses after each FUI was set using the following formula:

$$\alpha = 90 \times \mathrm{FUI}/3{,}000$$

where α is the angle of extension, FUI is the FUI, and 3,000 is the duration of the MI performance with real-time sensory feedback in milliseconds. For instance, an FUI of 500 ms results in 15° of orthosis extension at each of the six FUIs.

Statistical analysis

Power calculations were performed based on the requirement that effects were assessed at the 5% alpha level with 80% statistical power. There is a consensus that for chronic stroke survivors, a minimum increase of 5.25 in their FMA-UE score is required for the therapy to be considered clinically meaningful (32). Therefore, the primary endpoint of the treatment was determined to be an average increase of 5.25 points in FMA-UE scores; the SD was assumed to be 4 points based on evidence from the available literature (22). In the absence of information concerning the magnitude of the correlation between pre- and posttreatment scores, a worst-case scenario was adopted whereby the correlation was set to zero. Under these assumptions, the study required a sample of 12 stroke survivors.

For each of the outcome measures, we compared the scores recorded at three time points: (i) before taking part in the study, (ii) right after finishing the trials, and (iii) 4–6 weeks after completion. To assess the effect of neurofeedback training, we employed repeated measures of one-way ANOVA (RM-ANOVA) or its

non-parametric equivalent, the Friedman test, when the assumptions of ANOVA were not met. RM-ANOVA necessitates the satisfaction of two assumptions: linearity and sphericity. Given our relatively small sample size, we initially conducted a visual examination using the normal Q–Q plot to evaluate linearity. If no significant outliers were identified, we verified the linearity assumption using the Shapiro–Wilk test for each pre-, post-, and follow-up measurements. We applied the Greenhouse–Geisser method for testing and correction if the sphericity assumption was violated. This method calculates an epsilon value, which equals 1 only when the sphericity assumption holds. In instances of sphericity violation, the epsilon value falls between 1 and $1/(k-1)$, where k represents the degrees of freedom of time, which was 3 in our study. In Prism 10, the Greenhouse–Giesser's correction is implemented by multiplying the epsilon value with the degrees of freedom used in calculating the RM-ANOVA's F-value.

For post hoc analysis following RM-ANOVA, in the event of a statistically significant treatment effect (F-statistic), we conducted pairwise comparisons between pre vs. post and pre vs. follow-up using the Sidak test to correct for multiple comparisons. Similarly, if the Friedman statistic demonstrated statistically significant differences, we performed a pairwise post hoc analysis comparing pre vs. post and pre vs. follow-up using Dunn's pairwise z test and corrected for multiple comparisons.

An exception was made for the RTMs for both the affected and the intact hands, where we had six groups of weekly average RTMs. Instead of comparing pre vs. post and pre vs. follow-up, we compared data from week 1 as the benchmark with each of the following 5 weeks (weeks 2–6).

We also measured the pre- vs. posttraining effect size for tests that showed significant changes. Considering the small sample size, we used Hedge's corrected version of Cohen's d (46), which reduces the effect size for small samples.

We conducted all statistical analyses using GraphPad Prism 10 software except for calculating the effect sizes for which we used Microsoft Excel 2019.

Conclusion

This study presents compelling evidence for the efficacy of a novel BCI therapy in promoting hand movement recovery among stroke survivors. Our findings demonstrate significant improvements in motor function, functional tasks, grip and pinch strength, reaction time, and neglect symptoms. These outcomes hold clinical relevance, surpassing clinically significant thresholds and reflecting measurable changes in patients' lives. The subjectively reported goal achievements further underscore the practical value of the studied solution.

While further research with larger sample sizes and rigorous controls is warranted, our study provides an important step towards harnessing the potential of BCIs in stroke rehabilitation. Our method offers a personalized and adaptable approach to neurofeedback training, addressing the unique needs of individual patients. With ongoing research to explore and refine its innovative therapy, it holds the promise of becoming an important tool in the rehabilitation toolkit, ultimately improving stroke survivors' lives and enhancing their recovery journey.

Acknowledgments

The authors thank Dr Stuart Howell for his valuable help with the calculation of the sample size required for this research.

Supplementary Material

Supplementary material is available at *PNAS Nexus* online.

Funding

This research was partly funded by the Entrepreneurs' Programme —Accelerating Commercialisation Grant (reference no.: AC000141).

Author Contributions

S.D. designed the study and drafted the manuscript. A.D.G. designed the study, performed research, edited the manuscript and supervised the study. A.H-B. and S.K. designed the study and edited the manuscript. M.B. designed the study, analyzed the data, edited the manuscript and supervised the study. D.A. designed the study, edited the manuscript, and supervised the study. All authors gave their final approval for publication.

Data Availability

The deidentified results for all outcome measures obtained from all available participants are shared on Figshare and may be accessed via the following DOI: 10.6084/m9.figshare.25997992.

References

1 Muellbacher W, *et al.* 2002. Improving hand function in chronic stroke. *Arch Neurol*. 59:1278–1282.
2 Fregni F, Pascual-Leone A. 2006. Hand motor recovery after stroke: tuning the orchestra to improve hand motor function. *Cogn Behav Neurol*. 19:21–33.
3 Raghavan P. 2015. Upper limb motor impairment after stroke. *Phys Med Rehabil Clin N Am*. 26:599–610.
4 Gündüz OH, Toprak CŞ. 2019. Hand function in stroke. In: Duruöz M, editor. *Hand function: a practical guide to assessment*. Cham (Switzerland): Springer. p. 125–135.
5 Winters C, van Wegen EEH, Daffertshofer A, Kwakkel G. 2015. Generalizability of the proportional recovery model for the upper extremity after an ischemic stroke. *Neurorehabil Neural Repair*. 29:614–622.
6 Feigin VL, *et al.* 2022. World Stroke Organization (WSO): global stroke fact sheet 2022. *Int J Stroke*. 17:18–29.
7 Kollen B, Kwakkel G, Lindeman E. 2006. Functional recovery after stroke: a review of current developments in stroke rehabilitation research. *Rev Recent Clin Trials*. 1:75–80.
8 Pichiorri F, *et al.* 2015. Brain–computer interface boosts motor imagery practice during stroke recovery. *Ann Neurol*. 77:851–865.
9 Ang KK, *et al.* 2014. Brain-computer interface-based robotic end effector system for wrist and hand rehabilitation: results of a three-armed randomized controlled trial for chronic stroke. *Front Neuroeng*. 7:30.
10 Frolov AA, *et al.* 2017. Post-stroke rehabilitation training with a motor-imagery-based brain-computer interface (BCI)-controlled hand exoskeleton: a randomized controlled multicenter trial. *Front Neurosci*. 11:400.
11 Ramos-Murguialday A, *et al.* 2013. Brain–machine interface in chronic stroke rehabilitation: a controlled study. *Ann Neurol*. 74:100–108.
12 Buch E, *et al.* 2008. Think to move: a neuromagnetic brain-computer interface (BCI) system for chronic stroke. *Stroke*. 39:910–917.

13 Caria A, *et al.* 2011. Chronic stroke recovery after combined BCI training and physiotherapy: a case report. *Psychophysiology*. 48: 578–582.
14 Ang KK, *et al.* 2011. A large clinical study on the ability of stroke patients to use an EEG-based motor imagery brain-computer interface. *Clin EEG Neurosci*. 42:253–258.
15 Broetz D, *et al.* 2010. Combination of brain-computer interface training and goal-directed physical therapy in chronic stroke: a case report. *Neurorehabil Neural Repair*. 24:674–679.
16 Shindo K, *et al.* 2011. Effects of neurofeedback training with an electroencephalogram-based brain-computer interface for hand paralysis in patients with chronic stroke: a preliminary case series study. *J Rehabil Med*. 43:951–957.
17 Daly JJ, *et al.* 2009. Feasibility of a new application of noninvasive brain computer interface (BCI): a case study of training for recovery of volitional motor control after stroke. *J Neurol Phys Ther*. 33: 203–211.
18 Ang KK, *et al.* 2015. A randomized controlled trial of EEG-based motor imagery brain-computer interface robotic rehabilitation for stroke. *Clin EEG Neurosci*. 46:310–320.
19 Belardinelli P, Laer L, Ortiz E, Braun C, Gharabaghi A. 2017. Plasticity of premotor cortico-muscular coherence in severely impaired stroke patients with hand paralysis. *Neuroimage Clin*. 14:726–733.
20 Kasashima-Shindo Y, *et al.* 2015. Brain-computer interface training combined with transcranial direct current stimulation in patients with chronic severe hemiparesis: proof of concept study. *J Rehabil Med*. 47:318–324.
21 Guggenberger R, Heringhaus M, Gharabaghi A. 2020. Brain-machine neurofeedback: robotics or electrical stimulation? *Front Bioeng Biotechnol*. 8:639.
22 Cervera MA, *et al.* 2018. Brain-computer interfaces for post-stroke motor rehabilitation: a meta-analysis. *Ann Clin Transl Neurol*. 5:651–663.
23 Darvishi S, *et al.* 2017. Proprioceptive feedback facilitates motor imagery-related operant learning of sensorimotor β-band modulation. *Front Neurosci*. 11:60.
24 Darvishi S, Gharabaghi A, Ridding MC, Abbott D, Baumert M. 2018. Reaction time predicts brain–computer interface aptitude. *IEEE J Transl Eng Health Med*. 6:2000311.
25 Darvishi S, Ridding MC, Hordacre B, Abbott D, Baumert M. 2017. Investigating the impact of feedback update interval on the efficacy of restorative brain–computer interfaces. *R Soc Open Sci*. 4: 170660.
26 Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. 1975. A method for evaluation of physical performance. *Scand J Rehabil Med*. 7:13–31.
27 Yozbatiran N, Der-Yeghiaian L, Cramer SC. 2008. A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair*. 22:78–90.
28 Azouvi P, *et al.* 2003. Behavioral assessment of unilateral neglect: study of the psychometric properties of the Catherine Bergego Scale. *Arch Phys Med Rehabil*. 84:51–57.
29 Bohannon RW, Smith MB. 1987. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*. 67:206–207.
30 Turner-Stokes L. 2009. Goal attainment scaling (GAS) in rehabilitation: a practical guide. *Clin Rehabil*. 23:362–370.
31 Cramer SC, *et al.* 1997. A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke*. 28:2518–2527.
32 Page SJ, Fulk GD, Boyne P. 2012. Clinically important differences for the upper-extremity Fugl-Meyer scale in people with minimal to moderate impairment due to chronic stroke. *Phys Ther*. 92: 791–798.
33 Van der Lee JH, *et al.* 2001. The intra-and interrater reliability of the action research arm test: a practical test of upper extremity function in patients with stroke. *Arch Phys Med Rehabil*. 82:14–19.
34 Cumming TB, Brodtmann A, Darby D, Bernhardt J. 2012. Cutting a long story short: reaction times in acute stroke are associated with longer term cognitive outcomes. *J Neurol Sci*. 322:102–106.
35 Samėnienė J, Krišč iūnas A, Endzelytė E. 2008. The evaluation of the rehabilitation effects on cognitive dysfunction and changes in psychomotor reactions in stroke patients. *Medicina (B Aires)*. 44:860.
36 Barker-Collo S, Feigin VL, Parag V, Lawes CMM, Senior H. 2010. Auckland stroke outcomes study: part 2: cognition and functional outcomes 5 years poststroke. *Neurology*. 75:1608–1616.
37 Murase N, Duque J, Mazzocchio R, Cohen LG. 2004. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol*. 55:400–409.
38 Bolognini N, Russo C, Edwards DJ. 2016. The sensory side of post-stroke motor rehabilitation. *Restor Neurol Neurosci*. 34:571–586.
39 Bassolino M, *et al.* 2022. Body and peripersonal space representations in chronic stroke patients with upper limb motor deficits. *Brain Commun*. 4:fcac179.
40 Kim T, Kim S, Lee B. 2016. Effects of action observational training plus brain–computer interface-based functional electrical stimulation on paretic arm motor recovery in patient with stroke: a randomized controlled trial. *Occup Ther Int*. 23:39–47.
41 Leeb R, *et al.* 2016. BCI controlled neuromuscular electrical stimulation enables sustained motor recovery in chronic stroke victims. Proceedings of the 6th International Brain-Computer Interface Meeting; Asilomar Conference Grounds, Pacific Grove, California, USA.
42 Kattenstroth J-C, Kalisch T, Kowalewski R, Tegenthoff M, Dinse HR. 2013. Quantitative assessment of joint position sense recovery in subacute stroke patients: a pilot study. *J Rehabil Med*. 45: 1004–1009.
43 Darvishi S, inventor; Rehabswift Pty Ltd, assignee. 2021 Aug 19. Stroke rehabilitation method and system using a brain-computer interface (BCI). US patent application 17/265,235.
44 Pfurtscheller G, Aranibar A. 1977. Event-related cortical desynchronization detected by power measurements of scalp EEG. *Electroencephalogr Clin Neurophysiol*. 42:817–826.
45 Marple SL Jr. 1987. *Digital spectral analysis with applications*. Englewood Cliffs (NJ): Prentice-Hall.
46 Hedges LV, Olkin I. 2014. *Statistical methods for meta-analysis*. Orlando (FL): Academic Press.