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Specifications and functional impact of a self-triggered grasp neuroprosthesis developed to restore prehension in hemiparetic post-stroke subjects

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Abstract

Background: Stroke is the leading cause of acquired motor deficiencies in adults. Restoring prehension abilities is challenging for individuals who have not recovered active hand opening capacities after their rehabilitation. Self-triggered functional electrical stimulation applied to finger extensor muscles to restore grasping abilities in daily life is called grasp neuroprosthesis (GNP) and remains poorly accessible to the post-stroke population. Thus, we developed a GNP prototype with self-triggering control modalities adapted to the characteristics of the post-stroke population and assessed its impact on abilities.

Methods: Through two clinical research protocols, 22 stroke participants used the GNP and its control modalities (EMG activity of a pre-defined muscle, IMU motion detection, foot switches and voice commands) for 3 to 5 sessions over a week. The *NeuroPrehens* software interpreted user commands through input signals from electromyographic, inertial, foot switches or microphone sensors to trigger an external electrical stimulator using two bipolar channels with surface electrodes. Users tested a panel of 9 control modalities, subjectively evaluated in ease-of-use and reliability with scores out of 10 and selected a preferred one before training with the GNP to perform functional unimanual standardized prehension tasks in a seated position. The responsiveness and functional impact of the GNP were assessed through a posteriori analysis of video recordings of these tasks across the two blinded evaluation multi-crossover N-of-1 randomized controlled trials.

Results: Non-paretic foot triggering, whether from EMG or IMU, received the highest scores in both ease-of-use (median scores out of 10: EMG 10, IMU 9) and reliability (EMG 9, IMU 9) and were found viable and appreciated by users, like voice control and head lateral inclination modalities. The assessment of the system's general responsiveness combined with the control modalities latencies revealed median (95% confidence interval) durations between user intent and FES triggering of 333 ms (211 to 561), 217 ms (167 to 355) and 467 ms (147 to 728) for the IMU, EMG and voice control types of modalities, respectively. The functional improvement with the use

of the GNP was significant in the two prehension tasks evaluated, with a median (95% confidence interval) improvement of 3 (− 1 to 5) points out of 5.

Conclusions: The GNP prototype and its control modalities were well suited to the post-stroke population in terms of self-triggering, responsiveness and restoration of functional grasping abilities. A wearable version of this device is being developed to improve prehension abilities at home.

Trial Registration: Both studies are registered on clinicaltrials.gov: NCT03946488, registered May 10, 2019 and NCT04804384, registered March 18, 2021.

Introduction

Stroke is the leading cause of acquired motor disability in adults [1] and the second cause of death worldwide after cardiovascular diseases [2]. The loss of hand opening function and fine motor control in the paretic upper limb remains an issue for more than half of stroke survivors [3] despite rehabilitation therapies and the emergence of new methods and approaches to improve the recovery of voluntary motor control [4–6]. Chronic deficits are particularly prevalent in the distal upper extremities, making extension of the fingers the motor function most likely to be impaired following stroke. As presented by Kamper and Rymer [7], this appears to result from a coactivation of the flexor and extensor muscles of the fingers, combined with a decreased voluntary excitability of the finger extensor muscles. Once in the chronic stages of recuperation, the plasticity of the brain decreases and motor recovery often plateaus [8, 9]. Post-stroke subjects usually develop compensatory behaviors, which further reduce the paretic hand usage and involvement in activities of daily living [10].

Restoring prehension abilities is challenging for individuals who have not recovered active hand opening capacities post-stroke [11, 12]. Certain strategies attempt to assist or substitute the impaired function using exoskeletons and orthoses [13], while others help restore and facilitate hand opening with functional electrical stimulation (FES) [14, 15] or hybrid orthoses [6, 16]. Exoskeletons provide the possibility for weight support and movement guidance, but are often too bulky for practical use [17] and require complex control strategies to assist user movements [18]. The smaller footprint and weight of FES devices provide the possibility for practical embedded devices that can be used autonomously by patients at home [19]. Thus, patients can continue their hand grasping rehabilitation by themselves in ecological conditions even in chronic stages [8, 20, 21]. However, FES alone can be insufficient to fully open the hand in some cases with limited selectivity and spastic hypertonia in the finger flexors, especially if hypertonia increases during stimulation [16, 22, 23]. Furthermore, FES alone does not provide support for arm stabilization, movement guidance and the lifting of objects [16]. These devices, using FES applied to finger extensor muscles to restore grasping abilities in daily life, called grasp neuroprosthesis (GNP), currently remain poorly accessible to the post-stroke population [24] because of the few devices marketed and specifically adapted to this population [25].

The H200 from Bioness, formerly known as the NESS Handmaster [20], and as of 2022 the ReGrasp from Rehabtronics, formerly known as the bionic Glove [26], are the only wearable, self-triggered upper limb FES devices currently available commercially for prehension assistance in a functional setting [25]. Once fitted on the patient, these

orthotic devices can be triggered on demand with a wireless button for the H200 and with head motion detected through an earpiece for the ReGrasp. However, the rigid orthosis of the H200, encompassing the wrist and the palm of the hand, limits adaptation to the patient's needs and the triggering method requires involvement of the non-paretic hand, limiting its usability in activities of daily living. Regarding the ReGrasp device, which currently remains only available in the USA, only head motion detection is proposed in addition to tapping on the device as control modalities, which can limit adaptability to some user's needs. More control modalities are required to increase acceptance and usability of these devices in patient's daily lives. Historically, GNP with adapted control modalities have been mostly developed and made available for the spinal cord injured tetraplegic population [27–29], but are still not widely available due to difficulties in commercializing such devices [25]. Furthermore, the pathological neurological context of brain lesions in the stroke population makes direct transposition of these devices impractical or even impossible [30, 31]. This is due to the appearance of neurological disorders such as spastic co-contractions, synkinesis, attention and planning deficits. In the stroke population, voluntary contraction of hand opening muscles often generates co-contractions of the antagonistic flexor muscles, effectively preventing the hand from opening [7, 30, 32]. This makes the use of some of the most promising control strategies for user intent detection such as electroencephalography of the motor cortex or electromyography (EMG) of the targeted muscle residual activity very challenging [22, 31]. Although some studies show promising results with electroencephalography or EMG-controlled FES, they either take place in very controlled environments [33], have a timing cue for participants to start the grasping tasks [34], or apply a manual trigger button to enable or disable intent detection to avoid unwanted triggering [35]. These approaches, although valuable for rehabilitation, have yet to demonstrate practical feasibility for use in more ecological conditions. Indirect control modalities must be developed for stroke subjects in order to avoid these specific difficulties.

This article presents a grasp neuroprosthesis design with a panel of control modalities made available to post-stroke hemiplegic participants (EMG activity of a pre-defined muscle, IMU motion detection, foot switches and voice commands). The first aim was to evaluate and obtain feedback from participants on each control modality in order to determine which are the easiest to use, and the most reliable and acceptable for use in ecological conditions. The second goal was to assess the responsiveness and latencies of the system during functional tasks with the selected control modalities. Finally, we studied the functional impact of such a self-triggered GNP through standardized prehension tasks performed with and without the GNP.

Results

Participants

Twenty-two participants who had hemiplegia following strokes were included between July 2019 and August 2022 (11 in the Prehens-Stroke 1 study and 11 in the Prehens-Stroke 2 study). The delay since stroke onset ranged from 2 months to 17 years, of which 64% were ischemic strokes. The paretic side was the right side in 59% of cases and 59% of participants were males. The median Fugl-Meyer Assessment for Upper Extremity score

was 29.5 out of 66 and ranged from 6 to 48. See supplemental data 1 for detailed participant information.

The refractory periods used by the participants on their chosen control modality, defining the minimum time between two successive control modality activations and hence their ability to quickly re-trigger FES, had a median duration of 1 s (95CI 0.5 to 2). The stimulation intensities, adjusted empirically by the investigators to obtain functional muscle contractions without inducing discomfort, for each pair of electrodes used, had a median of 17.5 mA (95CI 5 to 43). See supplemental data 2 for detailed participant refractory delays and stimulation intensities. FES-induced functional palmar grasp was made possible with the additional pair of electrodes in 4 out of 22 participants, while for the other 18 participants, the thumb–index key-pinch was used to perform the evaluated tasks.

Modality evaluations

In the Prehens-Stroke 1 study, the Friedman test showed significant differences in both ease-of-use ($P < 0.001$) and reliability ($P < 0.001$) scores (Fig. 1A). Wilcoxon signed-rank tests with a Bonferroni adjusted P-value of 0.007 showed that for ease-of-use, apart from IMU head inclination that was not found significantly different from EMG paretic tibialis anterior, the three IMU head movement and EMG non-paretic tibialis anterior modalities were all found significantly different from the EMG paretic tibialis anterior and both foot switch modalities (adjusted P-value < 0.007).

In reliability, the IMU head inclination and EMG non-paretic tibialis anterior modalities were found to be significantly different from both foot-switch modalities (adjusted P-value < 0.007). The EMG of the tibialis anterior from the non-paretic side was also found to be significantly different (adjusted P-value < 0.007) from the one on the paretic side in reliability scores.

Detection of head movement in the sagittal (flexion) and horizontal (rotation) axes, although easy to use, had poor reliability (Fig. 1A) due to being too easily triggered by spontaneous head movements of the subject associated with the diction of the words "yes" and "no" (false-positives) and were abandoned after the first study.

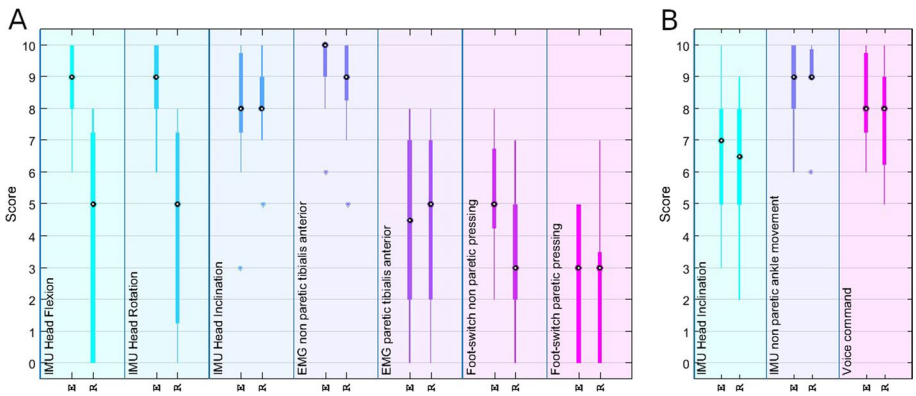

Fig. 1 Ease-of-use (E) and reliability (R) evaluations for all control modalities. **A** Seven modalities from the Prehens-Stroke 1 study ($N = 11$). **B** Three modalities from the Prehens-Stroke 2 study ($N = 11$). Scores range from worst imaginable (0/10) to best imaginable (10/10)

Dorsiflexion movements of the ankle and pressure on the foot switch on the paretic side were abandoned because when even possible for the participants, they were associated with synkinesis, limiting the opening of the paretic hand. The use of foot switches was abandoned altogether because their use was too complex for the participants and lacked reliability (Fig. 1).

On the non-paretic side, we also replaced the detection of the EMG of the tibialis anterior, which was too sensitive to the EMG electrode placement and to local skin condition, by the IMU detection of an ankle dorsiflexion movement.

In the Prehens-Stroke 2 study, the Friedman test only showed statistically significant differences in reliability scores ($P=0.009$). The reliability score of the IMU head inclination modality was found to be significantly lower than IMU non-paretic ankle movement (Bonferroni adjusted P-value of 0.017) (Fig. 1B).

GNP responsiveness and latencies

Comparisons of the duration of stimulations, assessed from the video recordings and from the logged data, showed a median difference of 9 ms (95 CI −82 to 220). The Wilcoxon signed-rank test of differences in the duration of stimulation between video assessment and from the logged data was found not to be statistically significant ($P=0.38$). This indicates a high level of synchronization between the two sources, confirming that both timelines can be reliably compared and analyzed.

The median frequency of the *NeuroPrehens* software's main processing loop was 502 Hz, corresponding to a sampling period, or refresh rate, of 2 ms (95CI 0.58 to 197).

The global analysis of self-triggering responsiveness and latencies of the GNP combining the three input types (IMU, EMG and voice command) as well as the two types of tasks (ball and cube) is illustrated in Fig. 2. According to the video assessment, the median duration from onset of stimulation to muscle contraction and full opening of the hand or fingers (opening phase) was 466 ms (95CI 194 to 682). The median duration from offset of stimulation to muscle relaxation and full closing of the hand or fingers (closing phase) was 216 ms (95CI 109 to 348).

The median responsiveness of the system, from the beginning of user intent to the stimulation being switched to On or Off, all three modality types combined, was 333 ms (95CI 152 to 715). Modality-specific median responsiveness were 217 ms (95CI 167 to 355) for EMG triggering (from non-paretic tibialis anterior muscle activity detection), 333 ms (95CI 211 to 561) for IMU triggering (from non-paretic foot dorsiflexion detection) and 467 ms (95CI 147 to 728) for voice triggering. The Friedman test did not reveal statistically significant differences between the responsiveness of the three types of modalities ($P=0.80$).

The median latency of the system, from the beginning of user intent to the intent being detected in the software, all three modality types combined, was 226 ms (95CI −13 to 600). The median latency specific to each modality was 209 ms (95CI −16 to 396) for EMG triggering, 206 ms (95CI 14 to 638) for IMU triggering and 336 ms (95CI 72 to 551) for voice triggering. The Friedman test did not reveal statistically significant differences between the latencies of the three types of modalities ($P=0.24$).

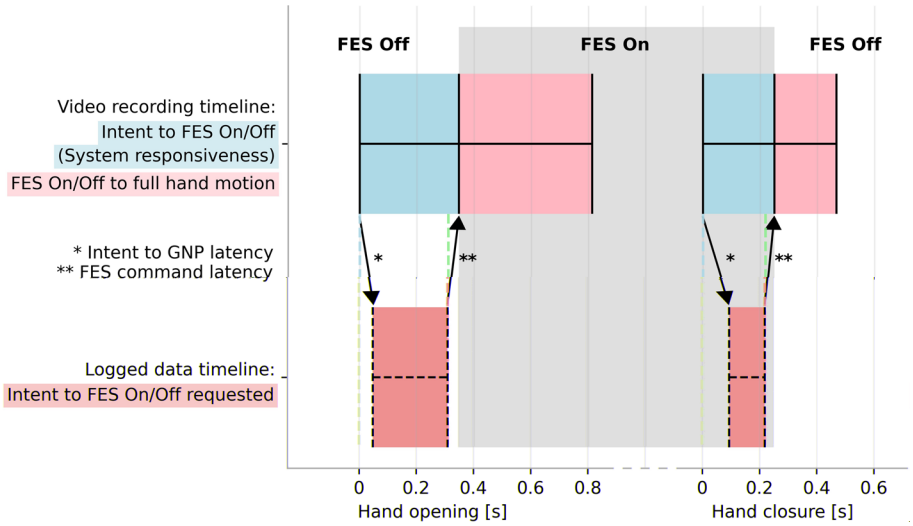

Fig. 2 Global self-triggering responsiveness and latencies of the GNP given as median durations. The hand opening phase corresponds to the beginning of user intent up to the complete opening of the hand due to stimulation, and the hand closure phase corresponds to the beginning of user intent up to the complete closure of the hand after deactivation of the stimulation. All three input types (IMU, EMG and voice command) as well as both types of tasks (ball and cube) are combined here for a synthetic representation. The gray background represents the time where FES is in effect. The blue boxes represent the system's median responsiveness, which is the duration between the beginning of user intent and the switching of FES to On or Off, as determined through video assessment. The green boxes represent the duration between the arrival of input data signaling user intent and the switching of FES to On or Off being requested by the GNP. The pink boxes represent the duration between visible onset/offset of stimulation and full hand opening or closing through video assessment. The (*) intent to GNP latency arrows are the previously presented modality latencies, while the (**) FES command latency arrows represent the duration between the request for the stimulation to be switched On or Off being performed by the software and it starting to take effect as detected from the video assessment

The median delay between FES commands being sent by the software and the effects on the muscles of the user starting to be effective and visible through video assessment was 101 ms (95CI − 177 to 314).

Functional improvement

The use of the GNP had a statistically significant impact on both tasks (Fig. 3). The median improvement on functional prehension abilities with the use of the GNP were of 2.0 points (95CI − 2.1 to 5) and 4.0 points (95CI 0 to 5), respectively, for task 1 and 2, while with both tasks averaged, the median improvement was of 3 points (95CI − 1 to 5) points. In tasks that had a score below 5 without the GNP, the use of the GNP allowed to improve tasks scores to 5 in 70% of cases.

Discussion

We presented a GNP using FES to assist paretic hand opening for functional improvement to post-stroke subjects with an incapacity to voluntarily open the hand. Of the nine indirect control modalities investigated in ease-of-use and reliability for self-triggering of the FES, three were identified as practical (lateral head inclination, non-paretic foot movement and voice control). All three input types showed a self-triggered GNP responsiveness below 500 ms confirming the good usability of the system to carry out

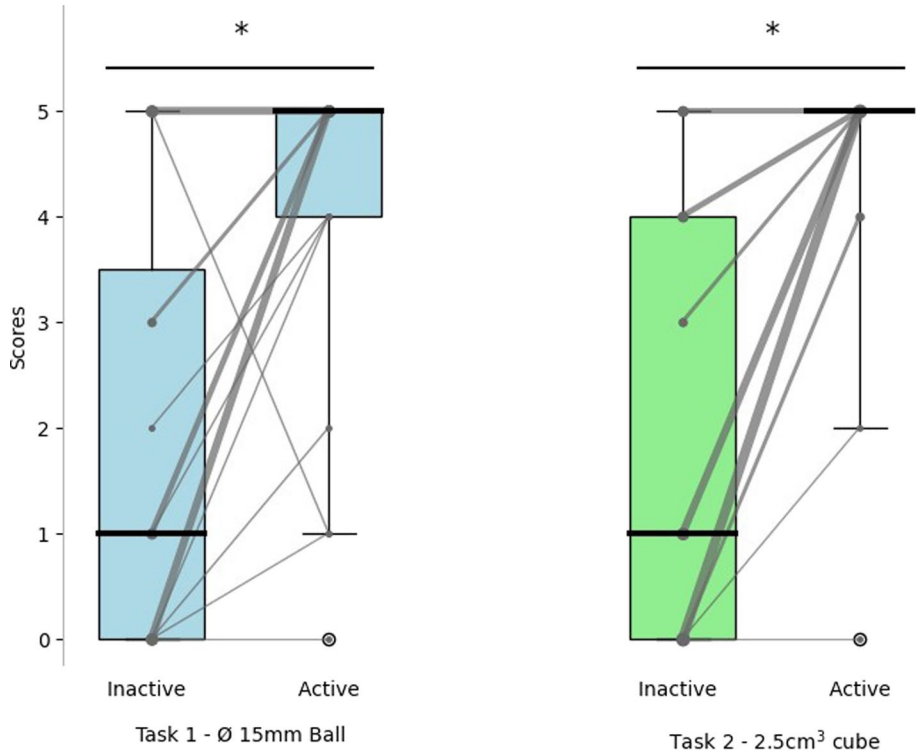

Fig. 3 Functional tasks scores of all participants with GNP active and inactive. Median values are shown in thick black horizontal lines. For each task, all 22 subjects were evaluated with (Active) and without (Inactive) the GNP. Asterisks above the tasks indicate significant differences with *P*-values < 0.025 (*P*-values equal to 0.0035 and 0.0003 for tasks 1 and 2, respectively) with a greater score when GNP was active. Gray lines link the pairs of values between inactive and active scores and get bigger for every identical pair of scores. Circled dots represent outliers

functional tasks. Finally, the use of GNP showed improvement in prehension abilities for the two functional tasks assessed.

Ease of use, reliability and overall acceptability of the GNP are crucial for autonomous home use, to prevent users from becoming discouraged and abandoning these devices [36, 37]. Hence, control modalities must be practical and adapted to the user's needs, according to their daily life situations. Moreover, sufficient responsiveness is required for practical use so that the system can be easily integrated by the user.

Which modalities to self-trigger the FES?

Whilst control modalities such as EEG intent detection [38] or EMG detection of residual muscle activity from voluntary contraction of the targeted muscles [39] are often used for the tetraplegic population, we focused on what could be considered as indirect modalities with the potential to be used in an ambulatory setting. These indirect control modalities were chosen because in the post-stroke population, voluntarily trying to open the paretic hand when hand opening capabilities have not been recovered frequently results in spastic co-contraction of the antagonistic finger flexor muscles [7, 23]. These co-contractions instead block hand opening and prevent prehension restoration devices from further assisting the hand opening [30, 31, 40]. Using indirect control modalities

such as voice control, IMU-based detection of specific motions of the head or of the non-paretic foot, in order to trigger FES of the paretic finger extensor muscles, enabled functional paretic hand opening while avoiding spastic co-contractions. Moreover, EEG in particular is impractical for autonomous home use by stroke patients and would require robust signal processing for reliable intent detection due to the brain lesion and the cortical reorganization following stroke, especially when considering ambulatory usage. Therefore, considering the neurological specificity of the post-stroke population, indirect control modalities are more practical for the restoration of prehension capabilities as they avoid the complications of spastic co-contractions and provide a more feasible approach for large-scale adoption of these technologies in the daily lives of stroke survivors with paretic-side prehension deficits.

In the first study (Prehens-Stroke 1), we investigated seven different modalities for self-triggering of the GNP. We retained the modality considered most practical and reliable (frontal movements of the head detected by IMU) for the second study (Prehens-Stroke 2) and modified a second trigger based on ankle dorsiflexion (EMG was abandoned in favor of IMU). The foot-switch pressing control modality was also abandoned in favor of the IMU detection of ankle dorsiflexion as having to find the foot-switch under the table with the foot was deemed impractical by the participants. While a wearable version of this foot-switch could have resolved this challenge, this was not investigated as the IMU detection of ankle dorsiflexion was deemed similar in function and more practical since it required less adaptations to the user's shoe. Due to requests from post-stroke subjects, we added voice control as a new possibility and re-investigated these three modalities in the second study. The results from both studies showed that motion detection of the head or the ankle through an IMU sensor were reliable and easy to use for all participants. The resulting consensus was that both IMU and voice were promising control modalities and should be available for switching, according to contextual preferences. However, most participants chose the IMU detection of ankle movement modality over the voice command because of the increased possibility of unwanted false-positives and false-negatives with voice control. False-positives and false-negatives rates of detection could not be recorded reliably across all control modalities and participants; therefore, they were not reported here directly. However, they were implicitly included in the scoring of ease-of-use and reliability for each modality. Quantifying these missed detections (false-negatives) and incorrect detections (false-positives) could allow for better insight into the user's choices and scores in future studies. Regarding the detection thresholds selected with each participant for the control modalities, once chosen during the testing session, they generally did not need further adjustment and were reused for subsequent sessions, allowing the participants to get used to reliably triggering them on demand.

Is the responsiveness of GNP sufficient for functional use?

In the field of neuroprosthetics and exoskeletons for amputees or patients with spinal cord injuries, to ensure a perception of responsiveness, reliability, and rapid response, it is considered that the system's responsiveness should not exceed 300 ms [41–43]. In healthy subjects, the time to complete a reach-to-grasp movement at a spontaneous speed is approximately 980 ms [44, 45]. However, it is significantly longer in post-stroke

subjects with upper extremity paresis and is estimated to be 1500 to 2500 ms [45, 46], depending on the subject's condition.

Global responsiveness and latency of the system and its different types of input sensors were assessed to provide an overview of the GNP's capabilities and evaluate the usability of the control modalities in practical conditions.

The global median latency of the system, between the estimated start of user triggering intent to this intent being detected by the GNP was of 226 ms (95CI −13 to 600) all modality types combined. The negative values in the given confidence intervals are explained by the assessment methods used for comparing the two timelines. The first one being based on the events being recorded and timestamped by the GNP. While the second timeline is based on visual estimation by an investigator, frame by frame on video recordings, of the apparition of events, such as the beginning of user intent or the start of hand opening or closing motion. This allowed for a non-systematic bias, potentially of a few video frames, in the accuracy of the evaluation of events through the video recordings. The duration between two video frames here being of 33 ms, this hence made it possible in a few outlier cases, when comparing both timelines, for the intent to be detected by the GNP before it was even estimated from the video recordings.

The global median responsiveness of the system between the estimated start of user triggering intent and the FES being switched On or Off was of 333 ms (95CI 152 to 715). Although participants noted the increased latency with voice control compared to foot triggering, they still deemed it responsive enough for practical use. The processing stages for the voice control modality were the main source of latency and variability in the responsiveness, due to the 2-s speech buffer and sub-optimal feature processing. Regarding the IMU and EMG based modalities, the delay mostly originated from the input data acquisition pipeline which came from the Delsys acquisition software hosted on a Windows virtual machine and then being sent to the *NeuroPrehens* control software on the main Linux operating system. In comparison, real-time responsiveness for neuroprosthesis control strategies in amputees and SCIs are approximately 500 ms [38, 47, 48] using Myoelectric [47], Electroencephalographic [38] and Magnetoencephalographic [48] signals. While this makes the responsiveness of the investigated GNP comparable to what is being used with amputees and spinal cord injury subjects, further investigation is needed regarding the user's perceived responsiveness of the device in the case of users who have been affected by stroke.

Functional impact of the GNP

Functional improvements were significant in the specific grasping tasks with a median improvement of 3 out of 5 when using the GNP. These functional improvements combined with an embedded system would allow users to involve the paretic hand more often in unimanual and bi-manual tasks in daily life. However, only hand opening was assisted by the FES and finger closing force might not be sufficient for some potential users to hold and move heavy objects. Furthermore, while the proposed scale for functional assessment of prehension capabilities is based on the ARAT scale, with a more detailed scoring system, this modified scale is still currently being validated regarding consistency between assessors.

Limitations and perspectives

While the setup and control modalities we proposed were evaluated as easy and reliable enough for practical use, this evaluation was performed in a clinical setting and needs to be tested in autonomous home use by the patients. Indeed, autonomous management of an embedded device such as a GNP can be challenging, especially for post-stroke subjects. To guarantee acceptability for embedded devices intended for autonomous home use, patient feedback needs to be integrated in the design stages. Aspects such as ergonomics, autonomy, adaptability, reliability and responsiveness are critical for practical usability and should be further investigated in daily life usage.

Furthermore, the functional improvements provided by the GNP were evaluated for standardized tasks used in clinical setting. To confirm that these functional improvements translate well to activities of daily living, personalized tasks relevant to each subject could be selected and assessed in ecological conditions.

One of the remaining challenges is arm support and motion assistance. Indeed, some post-stroke subjects have a limited voluntary shoulder and elbow range of motion which often hinders their ability to reach for objects and perform grasping from the paretic side. While the non-paretic hand can be used in a rehabilitation setting to support and guide movement, this is not practical in day-to-day life as it prevents bi-manual tasks. The paretic hand is therefore often left out of spontaneous grasping tasks. This could be improved with robotic assistance such as wearable exoskeletons and hybrid neuroprostheses that could help support the weight of the arm and assist with reaching objects and more generally improve paretic upper extremity range of motion.

Another challenge in practical conditions is the ability of users to reliably don the device with reproducible electrode placement. While we confirmed it was reproducible across sessions with the electrodes that were used, under the supervision of an investigator, it remains to be validated when performed by users in autonomy at home. This is critical for ensuring functional recruitment of the muscles targeted in the inclusion session by the clinical investigators. Wearable devices incorporated in sleeve garments or orthoses might provide a valuable solution to achieve reproducible donning for autonomous usage.

We think that grasp neuroprostheses are now a real possibility thanks to new devices, sensors and functional electrical stimulators, and hope that this study can highlight some of the challenges encountered so that post-stroke subjects will soon have devices commercially available to assist their prehension capabilities in day-to-day living.

Conclusions

We presented a GNP using FES to assist paretic hand opening for post-stroke subjects. Of the nine indirect control modalities investigated in ease-of-use and reliability for self-triggering of the FES, three were identified by the participants as practical (lateral head inclination, non-paretic foot movement and voice control) with sufficient reactivity to be used for functional tasks. Its use made it possible for subjects to carry out functional tasks that were not possible without it, confirming its usability.

However, this device was evaluated in a clinical setting and needs to be validated in ecological conditions, in autonomous use for activities of daily living. We are currently investigating this with a wearable version of the GNP.

Material and methods

Participants

As part of this study on the characteristics of the GNP, a total of 22 participants were recruited from two prospective randomized cross-over studies approved by the French national ethics committee: Prehens-Stroke 1 (ClinicalTrial.gov ID: NCT03946488; ID-RCB: 2018-A02144-51; 11 participants; completed) and Prehens-Stroke 2 (ClinicalTrial.gov ID: NCT04804384; ID-RCB: 2020-A01660-39; 11 participants; in progress). All participants gave written informed consent before they were included. The Prehens-Stroke 1 study took place at the hospital, with 3 sessions over 3 days. The initial inclusion visit is where the ARAT standardized prehension scale was performed without the GNP. In the second session, the participants successively tested and scored all the control modalities and trained with the preferred one. And in the final session, they performed the ARAT scale again, this time using the GNP. The Prehens-Stroke 2 study had a similar design, but included 2 additional training sessions after the selection of the preferred control modality. This was done to allow the participants to have more time integrate the use of the GNP into their prehension patterns, bringing the total number of sessions to 5 sessions over 5 days.

The main pre-defined clinical objectives of these 2 studies are not addressed in this work which mainly focused on the characteristics of the GNP (triggering modalities, responsiveness and latencies) developed through the 2 protocols. For the functional assessment, each patient is compared to him/herself on evaluations with and without the GNP.

To be eligible for inclusion, the FES had to allow sufficient opening of the fingers to restore function. Major cognitive deficits, aphasia or significant spatial neglect that would prevent the user from handling and using the device effectively were exclusion factors.

Setup

Data acquisition, recording, processing for user intent detection and stimulation triggering were performed in real-time on a dedicated computer (NUC Kit NUC8i7HVK, Intel, USA) by the *NeuroPrehens* software (Python 3.8) specifically developed in collaboration between the University Hospital of Toulouse and Inria (French National Institute for Research in Informatics and Robotics). The operating system was a Linux Ubuntu 20.04 LTS, on which the *NeuroPrehens* software was running. A Functional Electrical Stimulator (RehaMove 3, HASOMED, Germany, CE marked), connected in USB to the computer, was used to achieve muscle contractions upon user intent detection. Parametrization of the stimulator and switching stimulation On or Off was performed through HASOMED's ScienceMode serial communication protocol.

The choice of control modality depended on patient ability and preference (EMG activity of a pre-defined muscle, IMU motion detection, foot switches and voice commands). A multichannel Trigno Research System platform (Avanti IMU, Delsys Inc., Natick,

USA) was used to acquire EMG and IMU data wirelessly at sampling rates of 2000 Hz and 148 Hz, respectively. The proprietary Delsys Trigno Acquisition software, used for acquisition of the EMG and IMU data was running in a dedicated Windows 7 virtual machine environment using Oracle VM VirtualBox on the Linux system. The EMG and IMU data streams were then sent through UDP sockets to the *NeuroPrehens* software running on the Linux-based main operating system. The different sampling rates of the EMG and IMU data streams were synchronized through reading by packets of 27 and 2 samples, respectively, resulting in a 74 Hz maximum refresh rate from the point-of-view of the *NeuroPrehens* software. A clip-on USB stereo microphone (Andoer, Shenzhen, China), plugged into the computer and managed by the *NeuroPrehens* software, was placed on the participant's collar to record speech at a sample rate of 22,050 Hz. Four USB cameras (front, top, left and right point of views), acquiring 30 frames per second, were used to capture the user's performance on functional tasks, assessed in a deferred time by a blinded rater.

Surface hydro-gel self-adhesive stimulation electrodes (4×3 cm) were placed by a trained investigator on the participants' paretic forearm over the extrinsic finger extensor muscles (Fig. 4). The main pair of electrodes was placed over the abductor pollicis longus muscle to achieve thumb abduction and enable the user to perform a thumb–index key-pinch. When possible, for the participant for whom spastic hypertonia of the finger flexors did not prevent finger extension, a second pair of electrodes was placed over the common extensor muscle of the fingers to achieve extension of the fingers in order to allow for a palmar grasp. When thumb opposition was needed to improve thumb–index opening distance, an additional pair of electrodes was placed over the thenar eminence to recruit the opposing thumb muscle. For each pair of electrodes, both anode and cathode electrodes were placed next to one another across the targeted motor point, not considering the directional flow of current due to the stimulation pulses used being symmetrical biphasic pulses. The stimulation frequency used was 25 Hz and the phase widths of the biphasic symmetric stimulation pulses were of 200 µs. For each pair of electrodes used with a participant, stimulation intensity was progressively adjusted to reach a functional motor threshold (i.e., sufficient opening of the fingers to carry out the task) without inducing discomfort. If needed, an orthosis could be used to lock the wrist in a neutral position and avoid wrist extension due to unwanted stimulation of the carpal extensors. A pen was used to mark the chosen electrode positions in order to ensure reliable electrode placement across sessions.

Software

The developed software was designed in a modular way to allow the clinical investigators to enable and disable components as needed (Fig. 5). Once the modules are selected and started in the graphical user interface (GUI), real-time data visualization windows become available. A window dedicated to the clinician allows visualization of the raw data from the various sensors to ensure everything is working as intended, while another window displays the values and current thresholds of the selected control modalities as well as the status of the stimulation channels. This second window is intended for the participant and provides direct feedback on electrical stimulation triggering to facilitate training.

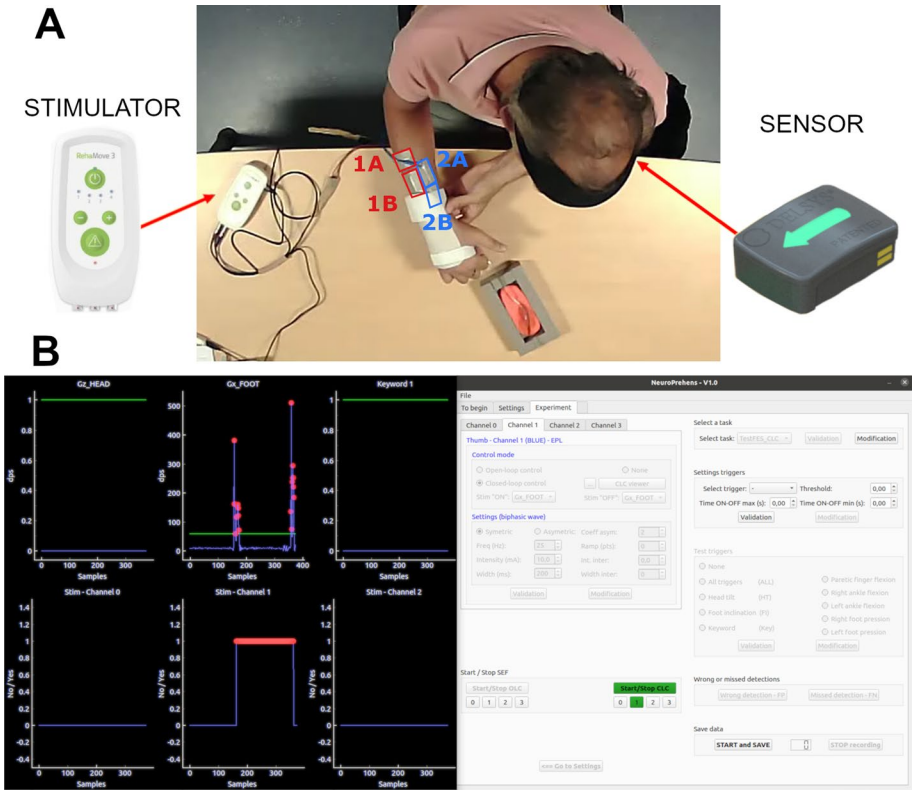

Fig. 4 Grasp neuroprosthesis setup. **A** A participant using an IMU sensor (Trigno Avanti, Delsys), highlighted on the right, placed with a headband on the back of the head, enabling them to self-trigger FES of their paretic finger extensor muscles through lateral inclination of the head in order to perform prehension tasks (here key-pinch on a spoon). The electrical stimulator used, highlighted on the left, was a commercially available, CE marked stimulator (Rehamove 3, Hasomed). Surface electrode positions for channel 1 in Red (opening of the fingers) and 2 in Blue (opening of the thumb) are highlighted with cathodes in position A and anodes in position B for each channel. While exact placement of the electrodes was subject dependent, this is a representative example following the described procedure. **B** Graphical user interface of the *NeuroPrehens* software, running on a dedicated Linux operated compact PC platform (NUC Kit NUC8i7HVK, Intel) allowing the clinical investigators to adjust the stimulation parameters, change the control modality to investigate and start or stop the recording (4 synchronized cameras and data log). Depending on the chosen control modality, a clip-on USB microphone, IMU or EMG sensor units (Trigno Avanti, Delsys) were placed on the participant. The data were recorded and processed by the *NeuroPrehens* software which enabled triggering of the electrical stimulation on demand, in real-time

The clinical investigator then has access to the stimulation parameters (i.e., frequency, amplitude and phase-width of each individual channel selected) and control modality' settings. For each control modality, these settings include the threshold value above which FES is triggered on the associated channels, the maximal stimulation duration, and a refractory delay to avoid multiple detections from the same attempt at triggering the FES.

Control modalities

For the first study (Prehens-Stroke 1), in order to investigate and identify the most suitable control modalities for intention detection in terms of ease of use by the subject and reliability, seven control modalities were presented to the participants. To avoid hindering bi-manual tasks and the triggering of spastic synkinesis and co-contractions of the

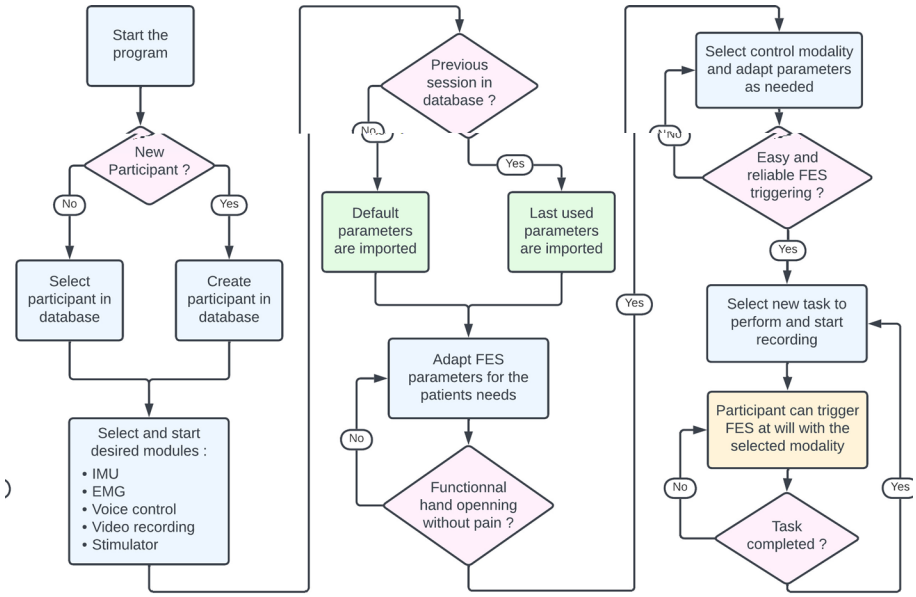

Fig. 5 Flowchart of the *NeuroPrehens* software. Schematic representation of the software stages and parametrization to fit the patient's needs and preferences to enable reliable self-triggered paretic hand opening using surface FES

paretic finger flexor muscles, we avoided all control modalities using the paretic upper limb, whether proximally or distally, either for arm motion detection or for the detection of muscle activity [30]. We included the following control modalities: EMG detection of tibialis anterior muscle contractions from the paretic or non-paretic sides, IMU detection from head movements in either of the three axes (placed with a headband below the external occipital protuberance) and a foot switch under the forefoot either on the paretic or non-paretic sides. After testing each control modality several times through the training sessions, with at least 5 to 10 repetitions performed with each possible control modality, participants selected their preferred one to use when performing the standardized prehension tasks on the last session.

In the second study (Prehens-Stroke 2), we only kept head movement in the frontal plane (inclination) because the movements in the two other axes, although reliable, were too easily triggered by spontaneous head movements of the subject associated with the diction of the words "yes" and "no" (false-positives). We chose the IMU detection of an ankle dorsiflexion movement on the non-paretic side, replacing the detection of the EMG of the tibialis anterior which was too sensitive to the EMG electrode placement and to local skin condition. Finally, voice command recognition was also added.

In both protocols, each modality was scored from 0 (worst imaginable) to 10 (best imaginable) by the participant for perceived ease-of-use and by the clinical investigator for reliability in intent detection. After the testing of each modality, to obtain the ease-of-use score, the participants were asked by the clinical investigator: "How would you rate the ease-of-use of this modality from 0, worst imaginable, to 10, best imaginable?".

When triggering intent was detected from the participant with the selected control modality, stimulation was switched from On-to-Off or from Off-to-On depending on the status of stimulation. The only exception was when stimulation triggering was still in

the refractory period following a previous detection, in which case the new intent detection was disregarded. This refractory period, between 0.5 and 2 s, was used to prevent unintentional multiple successive triggering and was adjusted to the needs of each participant and each modality. If the duration of stimulation exceeded the maximum of 60 s allowed, stimulation was automatically switched Off.

For intention detection through EMG signal (first study), the data were first filtered with a 4th order Butterworth bandpass filter (10–400 Hz). The signal was then rectified and a 4th order Butterworth low-pass filter at 9 Hz was then applied before computing the root mean square (RMS). This was done for each batch of 27 EMG samples, which corresponds to 13.5-ms windows at a 2-kHz sampling frequency. The result of the RMS was then compared to the threshold (i.e., a RMS value) selected for the participant. If the value was greater than the threshold, intent was considered as detected and stimulation was switched On or Off. The EMG threshold was determined for each participant as 60% of the detected RMS peak of EMG activity when they performed a voluntary contraction of the targeted muscle.

For intent detection through IMUs, whether it was accelerometric or gyroscopic, the data were filtered with a 4th order low-pass Butterworth filter at 3 Hz. After rectifying the samples, the highest value of the two latest samples was selected and compared to the threshold (i.e., value of acceleration in $m.s^{-2}$ or angular velocity in $deg.s^{-1}$). The IMU threshold was determined for each participant as 60% of the detected peak of acceleration or angular velocity when they performed the desired movement.

For intent detection through voice command, a word was first chosen with the participant to ensure it could be enunciated reproducibly, despite potential aphasia, while not being a word commonly used in everyday sentences, to minimize the likelihood of false-negatives and false-positives, respectively. After the participant selected a preferred word to be used as the keyword for intent detection, 15 to 30 enunciations of the chosen word spoken by the participant were recorded. Between 10 and 15 of these 2-s recordings were then selected to create a reference dataset, presenting variations such as intonation, volume and microphone positioning. The rates of change with first and second derivatives of a range of 30 Mel-Frequency Cepstrum Coefficients [49, 50] were then computed for each recording using the Librosa python library (also known as delta and delta-delta characteristics using the Savitzky–Golay filtering [51]) to represent speech features by focusing on the frequency bands most important to human hearing. The features obtained from these processing steps on each keyword recordings constituted the reference features for real-time voice recognition. The input microphone, with a sampling frequency of 22,050 Hz, was processed by chunks of 4096 samples, resulting in 186-ms windows. Each new batch of data was fed into a buffer containing the last 2 s of data and the feature computation steps used for the reference recordings were then repeated. The resulting set of features was compared to each set of reference features to find the closest match. The method used, known as dynamic time warping [50, 52], successively matches features from both the current buffer and reference recordings using sliding windows in a way that ignores time-dilatations which in speech correspond to changes in the speed of elocution. This algorithm outputs a value representing a notion of distance or dissimilarity between the two compared recordings. The lowest distance computed from comparisons with each of the reference recording's features was then

selected as the closest matching word. This distance value was then compared to the defined threshold, empirically adjusted by the investigator to the dataset of the participant, in order to detect when the specific keyword was spoken.

Latency and responsiveness analysis

The general responsiveness and latencies of the GNP were assessed by offline analysis and comparison between the video recordings and the data logged by the GNP. Although many sources of latencies are compounded and difficult to assess individually, a practical analysis and estimation of the latencies in the system provides an understanding of the system's responsiveness. This is important to interpret how the modalities are experienced by the users. High latencies and slow responsiveness of the system can affect the ease of use and the perceived reliability. The two main sources of input data used to provide the modalities of the GNP were a Trigno Avanti Delsys platform and a Lavalier type USB microphone.

The latency analysis was performed from two sources of data recorded by the *NeuroPrehens* software which logged snapshots of the system's status at each processing loop: (1) the current data samples and timestamps of each multiprocessing module as well as the status flags for intent detection and stimulation triggering; and (2) the video recordings from four USB cameras simultaneously controlled by the software. This setup enables a direct comparison between video recordings and logged data to estimate the latencies and responsiveness of the system.

The video recording was acquired with a 30-Hz frequency which provides a temporal resolution between frames of 33 ms. Visual inspection of the video recordings by a trained investigator allowed to visually estimate the start of the participant's triggering intent (from the movement of the head, the foot or the lips), the beginning of the finger motion (finger opening/closing) resulting from starting or stopping FES, and finally the moment when the hand completes the opening or closing movement. This constitutes what we will from now on be calling the video recording timeline. While performed by a trained investigator, the visual estimation of the times when the events occurred allowed for imprecisions in the timing assessment which is considered to be in the range of one to two video frames.

On the logged software data, we used two time-points, the beginning of user intent being detected from the sensor's data samples, and the moment at which stimulation was requested to be switched On or Off by the software, following the completed intent detection. This constitutes what we will from now on be calling the logged data timeline.

The refresh rate of the system's main processing loop was defined by the number of IMU, EMG or microphone packets processed per second depending on the selected control modality. The median sampling period of the main processing loop and its confidence interval of inter-sample durations were however also computed to evaluate sampling stability. To ensure synchronization between the video recording timeline and the software's logged data timeline, and to enable the comparative evaluation of the GNP system's responsiveness and latency, we compared the difference in FES duration between both timelines during the functional tasks.

To evaluate the responsiveness of the GNP system and the latency of its control modalities, each type of control modality (voice control, EMG and IMU detection) was

assessed in detail 8 times (4 openings, switching stimulation On and 4 closings, switching stimulation Off), to create a representative sample of stimulation triggering. The foot-switch detection method was not analyzed here because no patient chose this control modality in the first study and it was not offered in the second study. This analysis went from the beginning of user intent for opening of the hand with the triggering of stimulation On, extending the fingers, to the following user intent, triggering the stimulation Off and closing the hand.

A global analysis of the GNP's self-triggering responsiveness and latency was also performed by combining the results of all 24 assessments from the three types of control modalities (Voice control, EMG and IMU detection). This further enabled independent analysis of the GNP when triggering it for opening the hand, switching stimulation On, and for closing the hand, switching stimulation Off, with 12 openings and 12 closings assessed across the 3 types of control modalities.

The responsiveness was defined by the time from the start of user intent to the stimulation being switched On or Off. The latency was defined by the time from the start of user intent and the intent being detected by the software. Responsiveness and latency of the GNP were specifically analyzed for EMG triggering from the non-paretic tibialis anterior muscle (Prehens-Stroke 1), IMU triggering from the non-paretic ankle dorsiflexion movement and voice triggering (Prehens-Stroke 2).

Functional assessment

The functional improvements to the prehension capabilities were assessed using common standardized tasks from scales such as the Box and Blocks Test [53], and the Action Research Arm Test (ARAT) scale [54]. The participants tried to accomplish grasping, transporting and releasing of two objects, with and without using the GNP, following the ARAT guidelines with the standardized ARAT case. The two objects were a 2.5-cm3 cube and a 15-mm-diameter ball. The tasks were video recorded and later anonymized and blindly assessed by a trained occupational therapist.

However, the scoring method used in these standard scales are not adapted to the evaluation of fine improvements in prehension capabilities. The standard scoring system of the ARAT scale only differentiates the "inability to fully perform the task", or it taking an "abnormally long" time to perform [54] and hence does not allow for the evaluation of improvements in prehension quality during the grasping and releasing stages.

Consequently, we describe and use a scoring system designed to specifically isolate the exclusive analysis of grasping with its three phases: (1) *opening* is an active opening movement of the fingers (not achievable voluntarily by the subject, carried out with GNP) to position the object into the hand (for palmar grasp) or between fingers (for thumb–index key-pinch); (2) *grasping-moving* correspond to holding the object in the hand or between fingers (finger flexion movement performed voluntarily by the subject, without the aid of the GNP) against gravity during upper limb movements to move the object; (3) and *releasing* is an active opening movement of the fingers (not achievable voluntarily by the subject, carried out with the GNP), the thumb in case of a thumb–index key-pinch or all the fingers in case of a global palmar grasp, to release the object out of the hand. This scoring system is derived from the traditional Action Research

Arm Test to focus on the prehension component during unimanual grasping, independently of the quality and modality of the approach, with a score between 0 and 5:

- 0 = cannot perform the opening phase (active movement of finger aperture to insert the object in the hand or between the fingers) and requires passive insertion of the object;
- 1 = can partially perform the opening phase but insufficiently and requires passive insertion of the object;
- 2 = completely performs the opening phase, but cannot perform the grasping-moving phase (hold the object in the hand or between fingers against gravity during upper limb movements to move the object);
- 3 = completely performs the opening and the grasping-moving phases, but cannot perform the releasing phase (an active opening movement of the thumb in case of a thumb–index key-pinch or of all the fingers in case of a global palmar grasp to release the object from the hand) which requires an external assistance, either from the investigator or from the user's non-paretic hand, to remove the object from the hand;
- 4 = completely performs the opening and the grasping-moving phases, and partially performs the releasing phase (partial active opening of the hand linked to active extension of the fingers) which requires an external assistance to remove the object from the hand;
- 5 = completely performs the opening, grasping-moving and releasing phases.

The entire task had to be completed in less than 60 s. One retry was permitted after a failure. The duration of each task was timed from the start of the approach movement (the beginning of the hand's movement towards the object) to the release of the object (loss of contact between object and hand).

Statistical analyses

Due to the small sample sizes and the variability of measures, after Shapiro–Wilk tests and visual inspection, the data were not found to follow a normal distribution and were hence described with non-parametric statistical tests, medians and non-parametric 95% confidence intervals (95CI) using the lower and upper bounds of the data's ranked distribution (2.5% and 97.5% ranked percentiles).

Friedman tests were used to compare the 7 control modalities assessed in Prehens-Stroke 1 and the 3 modalities assessed in Prehens-Stroke 2 on both the perceived ease-of-use and the investigator assessment of reliability in intent detection (each modality was scored with a numerical scale from 0 to 10). Friedman tests were also used to compare responsiveness and latency (seconds) between IMU, EMG and voice commands. When significant differences were found, post hoc Wilcoxon tests were used to determine which conditions differed. To control the false discovery rate, for each significant Friedman test (P-value < 0.05), a Bonferroni procedure was performed to adjust the alpha risk threshold (P-value) for the n post hoc Wilcoxon tests with a significant P-value $< 0.05/n$.

The comparison of stimulation durations, assessed from the video recordings and from the logged data, were compared with a Wilcoxon test (significant if P-value < 0.05). The functional score with active GNP versus inactive GNP during the two functional tasks were compared with a Wilcoxon test (significant if P-value < 0.025 with Bonferroni adjustment).

Abbreviations

FES	Functional electrical stimulation
GNP	Grasp NeuroProsthesis
IMU	Inertial measurement unit
EMG	Electromyography
RMS	Root mean square

Supplementary Information

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Supplementary Material 1. Patient information for the Prehens-Stroke studies 1 and 2.

Supplementary Material 2. GNP settings and stimulation intensities for the Prehens-Stroke studies 1 and 2.

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Author contributions
Study conception and design were performed by D.G. with input from M.C., R.L.G. and C.A.C. Material preparation, and software development were performed by D.G. and R.L.G. Data collection was performed by D.G., J.F., M.C., R.L.G. and C.C. Blinded analysis of videos was performed by M.M. Data analysis was performed by R.L.G. and D.G. The ethical approvals for these studies were obtained by J.F. and D.G. The first draft of the manuscript was written by R.L.G. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. The study Prehens-Stroke 1 was supervised by J.F., C.A.C. being responsible for acquiring the financial funding. The study Prehens-Stroke 2 was supervised by D.G. who was further responsible for acquiring the financial funding.

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Availability of data and materials
Data are provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained by the French national ethics committee (Comité de Protection des Personnes (CPP) Nord-Ouest II for Prehens-Stroke study 1 (18.09.13.67709, ID-RCB: 2018-A02144-51) and Sud-Est IV for Prehens-Stroke study 2 (19.04.08.69902, ID-RCB: 2019-A00808-49). All procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and the subsequent amendments. The participants gave written informed consent prior to inclusion in the studies.

Consent for publication
The participants gave their consent for the recorded data to be used in publications.

Competing interests
The authors declare no competing interests.

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