

Upper Extremity Functional Rehabilitation for Stroke Survivors Using Error-Augmented Visual Feedback: Interim Results

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Abstract— Stroke rehabilitation is often terminated once a plateau in motor recovery is observed, but new training modalities have demonstrated that further functional improvement is possible after the onset of the chronic phase. In particular, feedback technologies augmenting error proved to foster the relearning process. Here we explore the possibility of a robot-free implementation of Error-Augmentation (EA), where only visual feedback is distorted. We present the interim results from our ongoing blinded, randomized, controlled clinical trial testing the efficacy of parallel bimanual reaching with visual EA. Subjects trained in the virtual environment in 45-minute sessions, three times a week, for three weeks, half with and half without EA. A blinded therapist performed clinical evaluations before, 1 week after, and two months after training. Available results showed that both groups significantly improved. An advantage in the treatment group could be tracked at all time points, but no statistical significance was detectable between groups. Gains in the two groups were found to be compatible with the results of previous studies using robots and may prove to have similar effectiveness without the need for a costly and complicated robotic device. One new finding was that EA caused significantly higher inter-trial variability.

I. INTRODUCTION

Stroke is one of the primary causes of disability in the current century, with more than 800000 people per year affected in the United States [1]. Two-thirds of these individuals survive the event, and half of these live on with chronic disabilities. Hemiplegia and hemiparesis are the most common chronic disabilities resulting from a stroke episode [2]. Despite the widespread practice to terminate inpatient stroke rehabilitation when a plateau in motor recovery is observed [3], novel modalities of therapy such as intensive repetitive practice [4], task-specific training [5], and interactive technologies [6-9] offer evidence of possible further functional improvements after the onset of the chronic phase, even years after a stroke [10]. Therapy that lasts past the initial plateau is believed to be of great importance, and there is a clear need for innovation from the technology that is available today.

Function is believed to be regained after injury through a process of neuroplasticity, where the brain reorganizes and reforms connections [11]. Several technology-facilitated interventions can leverage neuroplasticity: visuomotor distortions such as rotations and other transforms of the visual feedback [12-15], elevation of resistive forces [16], and accentuation of the trajectory errors [17] have proven to induce

learning. Moreover, error-driven learning is one of the paths for neuroplasticity skill acquisition [18-20]. Recent work from our group supports the idea that the proper manipulation of error signals during practice can foster learning in both stroke [17] and healthy [21] populations. In particular, significant improvement is found only when the movement of the subject is modified such that the original error is magnified, and not when it is reduced: “in simple terms, if one perceives a larger mistake, they learn more and faster” [22].

Prior work demonstrated advantages from administering Error-Augmentation (EA) to stroke subjects using a combination of haptic forces gently pushing the hand away from the pursuit target, and visual distortions displacing the cursor further away from the target [23-24]. Results showed that the synergic action of haptic and visual EA can speed up learning in stroke patients. However, the use of robotics makes such a rehabilitative technique costly, time-consuming in terms of setup, and requires an engineer to be present along with a therapist [25]. To overcome these drawbacks, here we have explored a robot-free approach with visual EA only, making use of a simple and cheap hand-tracking sensor.

As in [24], we focused on EA implemented during a bimanual reaching task consisting of simultaneous movements in parallel mode. In fact, bimanual training not only offers the possibility of self-rehabilitation and “solo” training, but it has also shown to be a valid rehabilitation technique for the recovery of the hemiparetic affected limb [26-30], with some research supporting the evidence that bimanual activities engage additional cortical areas of the brain [31-34]. Furthermore, functionally relevant training that requires the involvement of *both* hands is an important recovery goal for many patients.

A previous publication demonstrated the feasibility and safety of training with the virtual environment in analysis [22]. Here we continue the exploration with the aim of understanding if a haptic-free implementation can also enhance learning similarly to the haptic implementation of EA, allowing for self-directed enhanced therapy without the need for robots. Here, we report half-way results of this ongoing clinical study.

II. METHODS

The Northwestern University Internal Review Board approved this research study (STU00204661). Study participants were recruited from a registry of post-stroke individuals or from responses to local flyer postings. In a pre-evaluation session, each subject signed a consent form that conformed to Northwestern University guidelines. Experiments were carried out entirely at the Center for Neuroplasticity Laboratory at the Shirley Ryan Ability Lab.

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The study was registered on ClinicalTrials.gov (ID number NCT03300141) prior to initiation.

A. Subjects

This study targeted chronic stage stroke survivors. Only subjects who suffered a stroke more than 8 months prior to the experiments were considered. Other inclusion criteria were some recovery of proximal strength in the hemiparetic limb (upper extremity Fugl-Meyer score between 15-50); active elbow flexion and extension when the arm is supported against gravity; history of a single clinical hemispheric stroke event; age of 18 or over. While subjects suffering the following conditions were excluded: bilateral paresis; severe sensory deficits in the affected limb; severe spasticity or contracture; aphasia; cognitive impairment, or affective dysfunction that would influence the ability to perform the experiment (National Institutes of Health Stroke Scale (NIHSS), item n. 9 > 1); inability to provide informed consent; hemispatial neglect or visual field cut that would prevent subjects from seeing the targets (NIHSS, item n. 3 and n. 11 > 0); Botox injection to the affected upper extremity within the previous 4 months for focal tone management; concurrent participation in upper extremity rehabilitation; participation in previous, similar robotics intervention study. An expert occupational therapist assessed these criteria in a screening session. Subjects qualifying for the study were randomly assigned to two groups: the treatment group (or EA group) (N=7 in this paper), which trained with error-augmented visual feedback, or the control group (N=8 in this paper), which trained with veridical visual feedback. Group randomization was carried out in blocks of four at a time attempting to match the arm motor score of the Fugl-Meyer (AMFM) scale for the two groups. TABLE reports demographics, lesion information, and subjects' group. In this work, we summarize interim results from the first 15 subjects; however, further data collection is ongoing with the plan of collecting data from 30 subjects for completion of the clinical study.

TABLE I. PARTICIPANTS DEMOGRAPHICS AND GROUP. CONTROL (C), ERROR-AUGMENTATION (EA)

Participant ID	Sex	Age	Months Poststroke	Affected	Ischemic vs	Group
				Hemisphere	Hemorrhagic	
LG05	M	83	20	right	ischemic	C
LG06	F	27	49	right	hemorrhagic	C
LG07	F	42	27	right	ischemic	EA
LG08	M	64	85	left	ischemic	EA
LG10	M	82	14	right	hemorrhagic	EA
LG12	M	39	60	left	ischemic	C
LG15	M	59	38	right	ischemic	EA
LG17	M	63	64	Left	ischemic	C
LG19	M	48	69	left	ischemic	C
LG21	M	60	26	right	ischemic	C
LG22	M	48	199	right	hemorrhagic	C
LG23	M	52	72	left	ischemic	EA
LG24	M	53	67	Left	ischemic	C
LG25	F	61	72	left	unknown	EA
LG28	F	64	93	left	hemorrhagic	EA

B. Apparatus

The bimanual task was carried out in a three-dimensional virtual reality graphic system called the LookinGlass (Figure 1). The *LookinGlass* provided stereovision by means of three main components: a full HD 3D stereoscopic TV screen projects the stereographic image on a see-through half-silvered mirror, while active shutter glasses – synchronized to the TV via infrared - allow the subject to see in stereo. In this study, we chose to shutter the inferior screen so to occlude the vision of the arms: only two cursors representing the veridical or distorted position of the palm of the hands were shown moving in the virtual scene, allowing for visual feedback signal distortions. To track hands' motion, the *Leap*® Motion Controller hand-tracking sensor was positioned parallel to the ground on a rigid support under the hands of the subject. Finally, the software for the rehabilitative environment was implemented in *Python*, and *H3DAPI* was used to create the virtual scene.

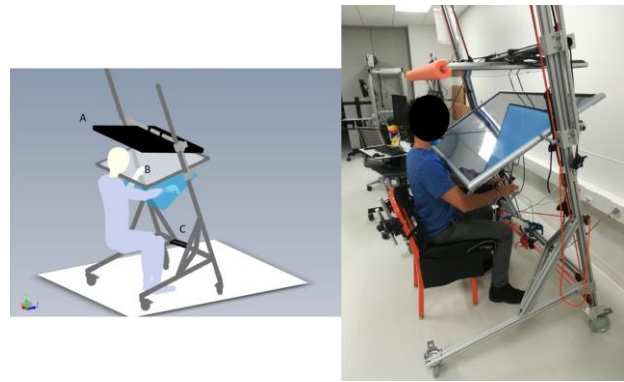


Figure 1. LookinGlass virtual reality system schematic (LEFT): A - 3D stereoscopic TV screen; B - half-silvered mirror; C - Hand-tracking sensor. Real system (RIGHT)

C. Protocol

Each subject trained in the virtual environment for three weeks, three times a week, for a total of nine sessions. Each session was composed of seven blocks of six minutes each, spaced out by two minutes of rest (or more if needed by the subject), such that little to no fatigue was reported. Each of the sessions lasted 50-60 minutes including resting time. In addition, subjects trained for 10 minutes during the pre-evaluation, post-evaluation, and follow-up (Figure 2).

During all sessions, participants were seated in a chair with both arms supported by a gravity-compensation orthotic. In the virtual environment, two cursors followed the movements of the left and right hands. Moving these cursors, the subject had to reach for the targets - represented by green spheres - with parallel movements. While carrying out the reaching movement, the subject also had to balance a ball rolling on a tray, so that non-simultaneous movements resulted in the ball falling from the tray. Each reaching movement started from a location virtually positioned above the center of the thighs. This position was unique for every subject: it was acquired through the hand-tracking sensor and then stored by the software of the system. The subject had ten seconds to carry out the reaching motion, after this time, the system suggested returning to the starting position. A target was considered reached only if the subject did not make the ball fall from the tray in the attempt of reaching. Each of the 15 pairs of targets

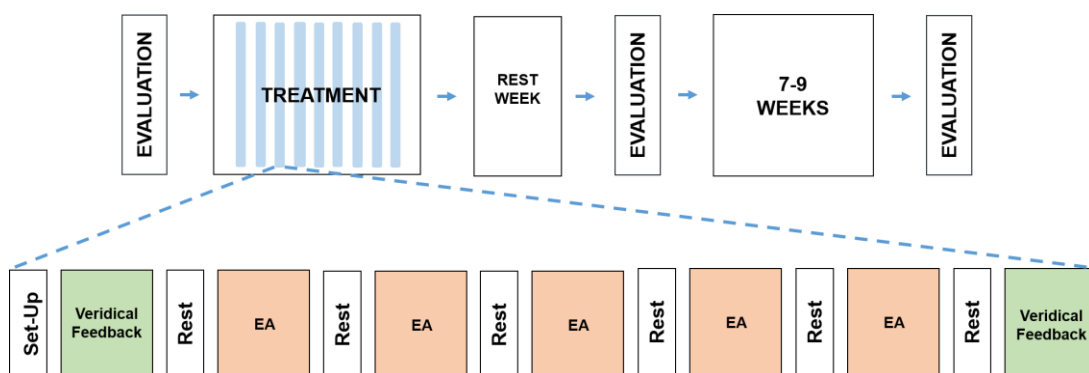


Figure 2. Study schematic (TOP) and single session protocol for the treatment group (BOTTOM) (NB. control group trained with veridical feedback in each block)

was placed equally distanced from the starting position in a virtual quarter sphere in front of the subject such that they covered evenly the reaching workspace. To make the task challenging, if a subject reached at least 70% of the targets in a block, the targets were moved 0.05 m away from the rest position in the following block. Conversely, if a subject's reaching success rate was less than 30%, targets were moved 0.05 m closer with respect to the resting position. Targets were presented randomly.

The treatment group trained with the distorted visual feedback described below in blocks numbers 2, 3, 4, 5, and 6 of each day (Figure 2). While the control group always trained with veridical feedback (i.e., never received EA). Each of the groups experienced the same amount of practice.

D. Error-Augmentation

As stated before, the joint effect of robotically applied error-augmenting forces and of visually augmented error has proven to have significant effects on clinical outcomes of hemiparetic stroke subjects [23-24]. However, in this work, the goal was to test the effects of visual EA only. For this sake, the definition of error was kept unchanged from the two mentioned studies. Error was defined as the instantaneous vector of the difference in position between the paretic hand and the healthy one plus the resting position of the participant. This vector was then multiplied by a factor 1.3 when the treatment was on: this means that the subject viewed the cursor relative to the paretic side in a position shifted from the real one such that the error in the execution of the task appeared visually greater than the true one.

E. Evaluations

Here we report both results based on clinical evaluations and results coming from trajectory data analysis through a measure of trajectory symmetry. For this purpose, subjects were evaluated both outside the LookinGlass, by the blinded therapist, and in the LookinGlass, carrying out 10 minutes of reaching with no EA applied. Evaluation occurred at three time-points: up to one week before the beginning of the treatment phase (pre-evaluation), a week after the last session of treatment to allow fatigue effects to vanish and evaluate short-term retention of benefits (post-evaluation), and seven to 9 weeks after the end of the treatment to evaluate long-term retention of benefits (follow-up). Unfortunately, at this phase of the study, follow-up data are available only for 8 out of the 15 subjects analyzed.

The primary clinical outcome for this study was the arm motor section of the Fugl-Meyer (AMFM), which gives a quantification of impairment of the hemiparetic limb [39]. Secondary clinical outcomes were the Wolf Motor Function Test (WMFT), which quantifies functional ability [40], and Box and Blocks assessment as an indicator of manual dexterity [39].

As encouraged by the balancing of the tray, the ideal execution of a bimanual parallel reaching task would result in parallel and simultaneous trajectories of the two hands. This is not a trivial task for a hemiparetic subject since an unbalance is present between the healthy side and the paretic one. By training in the presented system, a subject is expected to improve the ability of its paretic arm to perform movements resembling the ones of its healthy side. We focused on the instantaneous difference in position between the healthy and the paretic hand in the superior-inferior direction. Thus, to evaluate the quality of the movements of the paretic side while reaching for targets, we considered the maximum instantaneous difference in superior-inferior position of the two hands during a reaching movement and divided it for the distance reached. Since bigger errors are weighted downward for higher distances, we refer to this metric as Weighted Error (WE):

$$WE = \max_i(\text{abs}(z_{Li} - z_{Ri})) * \frac{1}{\text{reaching distance}}, \quad i = 1 : N \quad (1)$$

where N is the number of samples making part of a reaching movement and z_L and z_R are respectively the positions of the left and the right hand in the perpendicular direction of the sensor (i.e., superior-inferior direction).

F. Data Analysis

Position data were thresholded such that all data points for which the sensor read a position greater than 0.8 m in one of the three directions were eliminated: these points fall out of the reaching workspace and were considered readings errors. After this, data were resampled at 25 Hz using linear interpolation, and low pass filtered at 6 Hz. Considering only the part of the movement in which the subject is reaching out, the absolute distance between the two hands along the superior-inferior direction is computed for every data point. The maximum of these values is taken and divided for the reaching distance of the block to obtain one value of WE for every reaching movement.

To test for repetitive practice effects, an overall preliminary statistical analysis was carried out considering all subjects together: paired samples t-tests were performed between scores from first evaluation and post-evaluation and then, to examine for retention, between scores from first evaluation and post-evaluation. To test for treatment-related changes, both primary and secondary outcome measures were analyzed using a repeated measures ANOVA, with factors of time (pre, post, follow-up) and treatment type (EA vs. Non-EA). Post evaluation data, collected one week after the end of the treatment, allowed to evaluate effects of training without including fatigue, while follow-up data were collected to determine functional retention of benefits in the long term. All statistical tests were evaluated with a significance level of 0.05.

III. RESULTS

To date, data from 15 subjects, of which 8 in the control group and 7 in the EA group, are available. Fourteen subjects completed the post-evaluation session while only eight (5 controls and 3 EA) completed the follow-up session.

A preliminary analysis showed that all participants benefit from the repetitive training of the bimanual task, with an average overall gain pre-evaluation to post-evaluation of 3.0 ± 4.3 (mean \pm standard deviation, $N=14$) in AMFM (paired-samples t-test, $t(13) = -2.5910$, $p = 0.022$). Overall, effects seem to be retained over the 2 months with an overall significant gain in AMFM of 3.4 ± 2.3 (mean \pm standard deviation, $N=8$) between pre-evaluation and follow-up (paired-samples t-test, $t(7) = -4.1038$, $p = 0.0046$), however, more data for the follow-up evaluation are needed in order to have higher statistical power for this test. Group comparisons showed that, on average, the functionality of both the control and treatment groups improved with a Fugl-Meyer average increase in the post evaluation of 3.4 ($N=7$) for the treatment subjects and 2.6 ($N=8$) for the controls. As of post-evaluation results, only 8 subjects are available, with a Fugl-Meyer average increase of 4 ($N=5$) in the treatment subjects and 2.3 ($N=3$) in the control subjects (Figure 3). At this point, no significant interaction is found comparing the two groups (repeated measures ANOVA with factors of time and treatment type).

The change in the secondary measures was variable and both WMFT and Box and Blocks assessments did not show significant overall improvements. The WMFT functional

ability scale average gain between pre-evaluation and post-evaluation was 0.85 ± 5.3 (mean \pm standard deviation, $N=14$) while the average increase in the number of blocks transported in 60 seconds by the impaired hand was 1.7 ± 3.5 (mean \pm standard deviation, $N=14$). When testing for treatment-related changes, no significant interaction was found between the treatment type and time (repeated measures ANOVA with factors of time and treatment type). We found a significant p-value relative to the treatment factor for the Box and Blocks assessment: treatment and control groups were balanced based only on our primary outcome (AMFM). Besides, Box and Blocks assessment is a measure of manual dexterity, which is not the skill we are training directly in this experiment.

When analyzing the change in the custom-built metric of evaluation, a significant overall improvement was found, with an average overall decrease in *WE* of 0.076 ± 0.0915 points (mean change \pm standard deviation) for all participants over the three weeks from day-one of evaluation to post-evaluations (paired t-test, $t = 2.3438$, $p = 0.0277$). This overall effect was retained over the 2-months, with an improvement in *WE* between day-one and follow-up of 0.0753 ± 0.0375 (mean change \pm standard deviation) (paired t-test, $t = 2.2980$, $p = 0.0331$). A small advantage was seen in the treatment group, with no significant difference detected in the two groups either considering or excluding the outlier (Figure 3, middle and right). However, only data for 5 out of 8 controls and 6 out of 7 treatment subjects were available when considering the post-evaluation, while only 3 subjects per group completed the follow-up. Hence, failed significance might be due to insufficient numbers of subjects.

Figure 4 (left) shows results from our built-in measure, *WE*. Daily change in performance was evaluated during the first block of every session, which was always free of treatment. As shown, both groups presented high intrasubject and intersubject variability. However, one participant in the control group had an anomalous increase in *WE*, for this reason, we considered it as an outlier and conducted a second analysis excluding it. Once excluded, the plot suggested that EA induced more variability in performance while training, both within a single session (wings for 95% confidence interval of the mean are larger for the EA group than in the control group) and within different days (more regular decrease in *WE* for the control group). Thus, these two aspects were tested statistically. A significantly higher intrasubject

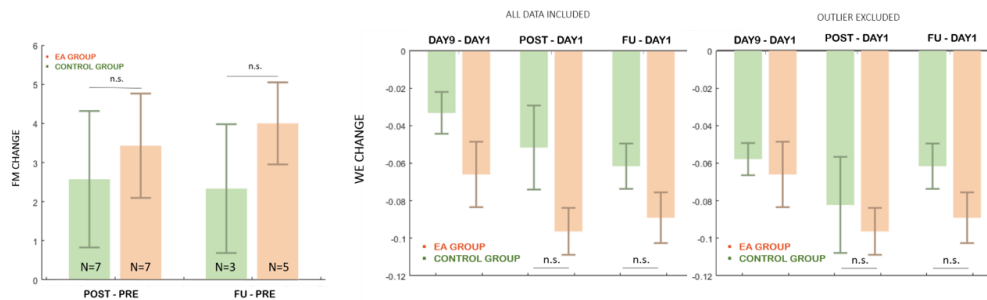


Figure 3. AMFM change (MEAN \pm SEM) from pre-evaluation to post-evaluation and follow-up (LEFT). WE change (MEAN \pm SEM) between day one of train and three time points: last day of training (DAY9), post-evaluation, and follow-up. All data are included (CENTER). The outlier in the control group is removed (RIGHT). An advantage can be tracked in the treatment (EA) group at all time points. Effects seems to be retained in the two-month period following the study. No statistical significance is found (repeated measures ANOVA with factors of time and treatment type); however, sample sizes are too small for a meaningful statistical analysis.

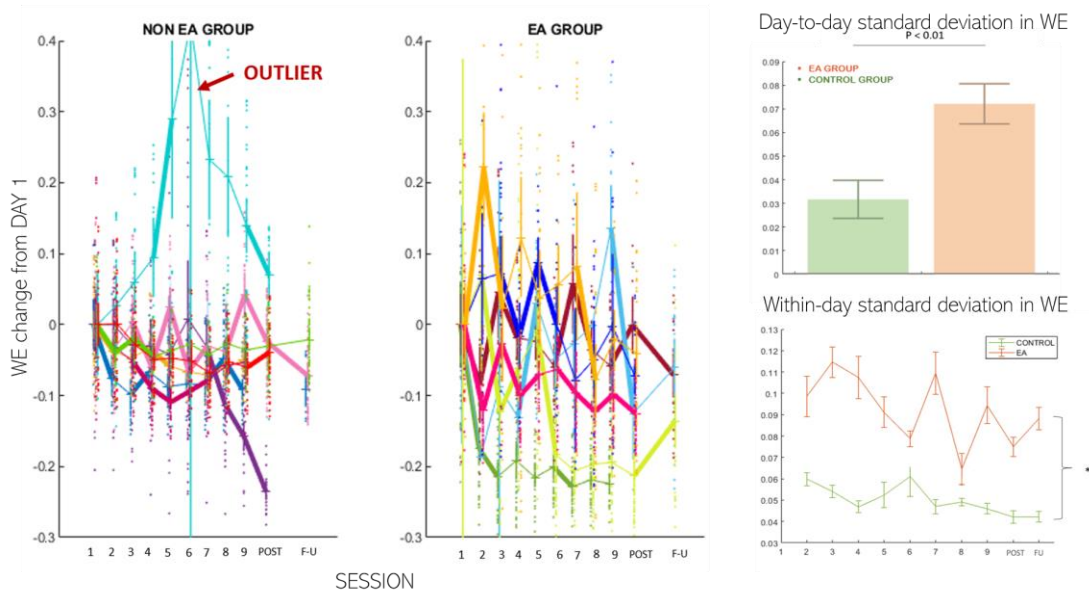


Figure 4. Weighted Error (WE) changes from the first visit for control group and EA group (LEFT). Each subject is shown in a different color. Mean of each day is represented as well as 95% confidence interval for the mean (wings) and single reaching scores (points). Thick lines show a significant change between the scores in two different visits (two-sample t-test). When the outlier is removed, EA subjects show more variability both within a day (wings) and day-to-day. Day-to-day standard deviation (MEAN \pm SEM) removing the outlier (RIGHT, UP). Statistical significance is found when removing the outlier from the control group (two-sample t-test, $t(12) = -3.08$, $P = 0.0095$). Intrasubject variability (i.e. SD) within each day (MEAN \pm SEM) (RIGHT, DOWN). Repeated measures ANOVA showed that treatment factor significantly interacts with the variability of the subjects within a single day, while the decrease in variability for both groups is not statistically significant.

day-to-day standard deviation was detected in the EA group when removing the outlier from the control group (effect size = 0.036 points of SD, two-sample t-test, $t(12) = -3.08$, $p = 0.0095$) (Figure 4, right, up). Figure 4 (right, down) also shows mean intrasubject variability within a day: even if for computing the WE metric all subjects were tested daily with no EA, subjects who trained with EA showed higher variability. ANOVA results suggested that within-day standard deviations were different for the two different treatments ($F(1,130) = 15.01$; $p = 0.0002$), while no interaction was detected between sessions of treatment and the within-day variability.

The baseline we considered for WE measure was the first block of the first day of training: during the pre-evaluation, in fact, only ten minutes were spent trying the task in the virtual environment, and none of the subjects received treatment. Thus, improvements between pre-evaluation and the first block of the first day of training were most likely due only to practice effect.

IV. DISCUSSION

We broke the blind to report halfway results from a blinded, randomized clinical trial to assess compatibility of visual error augmentation, compared to previous studies. Both AMFM and our built-in metric (WE) revealed that all participants, regardless of the treatment group, benefit from repetitive training of the parallel reaching task in the virtual environment. Even if the gain in the AMFM clinical score was modest, and one could possibly question its clinical relevance, it is possible that a meaningful effect size could be reached over a longer period of training. In fact, it is commonly believed that a minimum improvement of 3.5 AMFM points is needed for clinical relevance [43], while the overall significant

gain we obtained over the three-week intervention was of 3 points. Moreover, studies regarding interventions on chronic stroke subjects usually treat patients for periods longer or equal to six weeks [44] [8] [45] or involve more intensive practice [46], up to 6 hours of daily training [47], [48].

Importantly, gains in clinical scores were compatible with results from the previous studies on EA where subjects trained with a robot [22] [23]. This may suggest that the visual part of EA is the one needed for efficacy, but the hypothesis will have to be confirmed from the results of the complete study.

As in [24], only a very subtle and undetectable augmentation was administered to keep this study blinded. At this point, no significant effect of repetitive practice with EA over repetitive practice alone was detected neither looking at clinical outcomes nor at WE. An advantage could be tracked at all time points in the EA treated group for all metrics of evaluation, however, the sample sizes of each group were too small to carry out a relevant statistical analysis. In fact, from previous EA studies, one could estimate a variance of 2.5 [49] and arrive to a sample size of 15 individuals per group needed for a desired statistical power greater than 0.8.

In contrast with results coming from our primary outcome, when analyzing our secondary outcomes, we failed to find a significant overall improvement. This suggests that the bimanual task has greater impact on motor ability (assessed by AMFM) than on functional ability (assessed by WMFT). Thus, a functionally oriented task in combination with EA may be explored in future developments.

Thanks to our custom metric, WE, we could track daily changes in bimanual reaching ability. Its analysis shed light on some EA-induced effects that could not be observed in previous studies. In fact, training with distorted visual

feedback induced a significantly higher variability in the performance while reaching with veridical feedback. One hypothesis is that augmenting the error of the impaired side with respect to the healthy hand may create internal conflicts between arm controllers, thus confusing the nervous system. However, this destabilization may bring to a new and better equilibrium with a higher learning rate than veridical feedback. In fact, despite being an unwanted aspect in motor performance, it was recently found that movement-to-movement variability is associated with faster learning allowing wider exploration of one's motor range [50-51]. More data should allow a better understanding of this potential correlation between practice variability and recovery. It also remains to be seen whether there is a difference in the retention between training and training error-augmentation.

V. CONCLUSION

Visual EA on its own, implemented robot-free through a simple and cheap hand-tracking sensor, can have similar results to haptically implemented EA on upper extremity rehabilitation of the chronic stroke subject. At this point, results show similarity with those obtained through synergic action of haptic and visual EA. However, results from the complete study will allow better conclusions. Overall, the results obtained up to now have demonstrated that self-guided upper-extremity training can rehabilitate individuals in the chronic phase of recovery by improving motor ability. This type of training can be implemented through a much cheaper and intuitive system by replacing the robot with a simple hand-tracking sensor. Such a robot-free implementation of error-augmented rehabilitation may allow for a more accessible device. Finally, this bimanual therapy offers a tool for "solo" training facilitating high doses of rehabilitation that may be "homework" for patients'.

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