Exploring the Utilization of Startle as a Therapy Tool in Individuals with Stroke

by

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ABSTRACT

Stroke is a debilitating disorder and 75% of individuals with stroke (iwS) have upper extremity deficits. IwS are prescribed therapies to enhance upper-extremity mobility, but current most effective therapies have minimum requirements that the individuals with severe impairment do not meet. Thus, there is a need to enhance the therapies.

Recent studies have shown that StartReact -the involuntary release of a planned movement, triggered by a startling stimulus (e.g., loud sound)- elicits faster and larger muscle activation in iwS compared to voluntary-initiated movement. However, StartReact has been only cursorily studied to date and there are some gaps in the StartReact knowledge. Previous studies have only evaluated StartReact on single-jointed movements in iwS, ignoring more functional tasks. IwS usually have abnormal flexor activity during extension tasks and abnormal muscle synergy especially during multi-jointed tasks; therefore, it is unknown 1) if more complex multi-jointed reach movements are susceptible to StartReact, and 2) if StartReact multi-jointed movements will be enhanced in the same way as single-jointed movements in iwS. In addition, previous studies showed that individuals with severe stroke, especially those with higher spasticity, experienced higher abnormal flexor muscle activation during StartReact trials. However, there is no study evaluating the impact of this elevated abnormal flexor activity on movement, muscle activation and muscle synergy alterations during voluntary-initiated movements after exposure to StartReact.

This dissertation evaluates StartReact and the voluntary trials before and after exposure to StartReact during a point-to-point multi-jointed reach task to three different targets covering a large workspace. The results show that multi-jointed reach tasks are susceptible to StartReact in iwS and the distance, muscle and movement onset speed, and muscle activations percentages and amplitude increase during StartReact trials. In addition, the distance, accuracy, muscle and movement onsets speeds, and muscle synergy similarity indices to the norm synergies increase during the voluntary-initiated trials after exposure to StartReact. Overall, this dissertation shows that exposure to StartReact did not impair voluntary-initiated movement and muscle synergy, but

even improved them. Therefore, this study suggests that StartReact is safe for more investigations in training studies and therapy.

DEDICATION

I dedicate this dissertation to my fiancé, who is my family and best friend and to my parents and my sisters who supported me in life and had to be far from me for the last 6 years that I was here working on my PhD.

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CHAPTER 1

1 INTRODUCTION

1.1 Background and Significance

1.1.1 Stroke and Rehabilitation

In the U.S., stroke is the leading cause of long-term disability according to recent data [1]. One person every 40 seconds will suffer a stroke in the U.S. and it costs around $34 billion/year (including medical care, therapy, and missed days of work) [1]. Up to 80% of individuals with Stroke (iwS) have a loss of hand/arm control [2], making completion of daily activities not possible. Many iwS are prescribed rehabilitation after stroke, but even after therapy 65% of patients cannot use their impaired hand for their daily activities and ~63.5% of them never achieve more than a 90/226 Fugl-Meyer score. [3]–[6]. Most notably, individuals with severe impairment, who usually need the most rehabilitation, are not able to participate in the best therapeutic options. A recent review of clinical trials shows the most effective rehabilitation technique currently available is Constraint Induced Movement Therapy (CIMT) [7] (Figure 1). To be eligible for CIMT requires at least 10° wrist extension, 10° thumb abduction and 10° finger extension [8]. Therefore, individuals with severe impairment are not able to participate in our best therapies due to lower ranges of motion. Therefore, they use their impaired arm less, which means less muscle activation in that arm. The less muscle activation in the impaired arm leads to more spasticity [9] and therefore, eventually, the more spasticity leads to even lower ranges of motion. This vicious cycle makes quality of life decrease for these individuals with severe stroke and gives them no hope for improvement. The goal of this dissertation is to explore a new potential therapy to help these individuals. StartReact is a new potential therapeutic solution that is targeted at individuals with severe and moderate stroke.

Figure 1. Upper extremity impairment in iwS

1.1.2 StartReact

StartReact (SR) has recently been posed as a potential rehabilitation tool because of the way it influences movement in iwS. More than a simple reflex, SR movements maintain the spatial and temporal

features of planned movements [10]–[14] (Figure 2). SR is the fast, involuntarily release of a voluntarily planned movement via the classic startle reflex, which is triggered by the presentation of a loud and Startling Acoustic Stimulus (SAS) [13], [14]. To achieve SR, subjects must be fully prepared to move prior to being exposed to an SAS. The most accurate way to evaluate the presence of SR is by monitoring the Sternocleidomastoid (SCM) muscles at the left and right sides of the neck. The presence of SR is confirmed by a fast (less than 120 ms latency) right or left SCM muscle activation (SCM+) during a planned movement [14]–[16] (Figure 3).

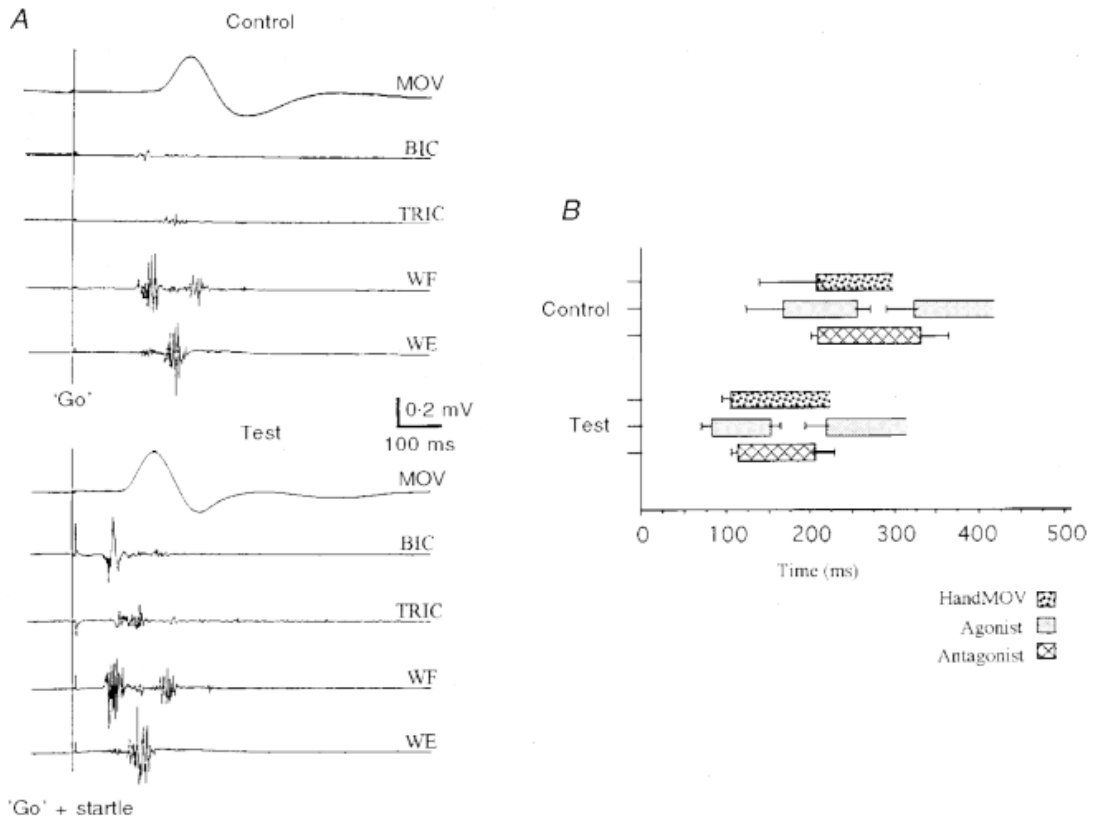

Figure 2. SR vs voluntary data example. EMG and movement data during voluntary-initiated movement (top left) and SR (bottom left) performing wrist flexion task. The left part shows the same movement but with faster initiation. The right figure shows group mean of muscle activations. The SR muscle activations are faster but has the same patterns of muscle activations as voluntary movement [14].

The startle reflex (Figure 3.C) is the body's response to some sudden and high intensity stimulus. Contrary to SR (Figure 3.B), there is no movement preparation during classic startle. Therefore, the reaction usually is observed as flexing the arms, blinking, jumping or no visible reaction in different people. Same as SR, the early SCM activation is present during the classic startle and it is implying that SR is engaged in the same pathway as startle reflex circuitry. However, there is argument about the mechanism and pathway of SR in the literature.

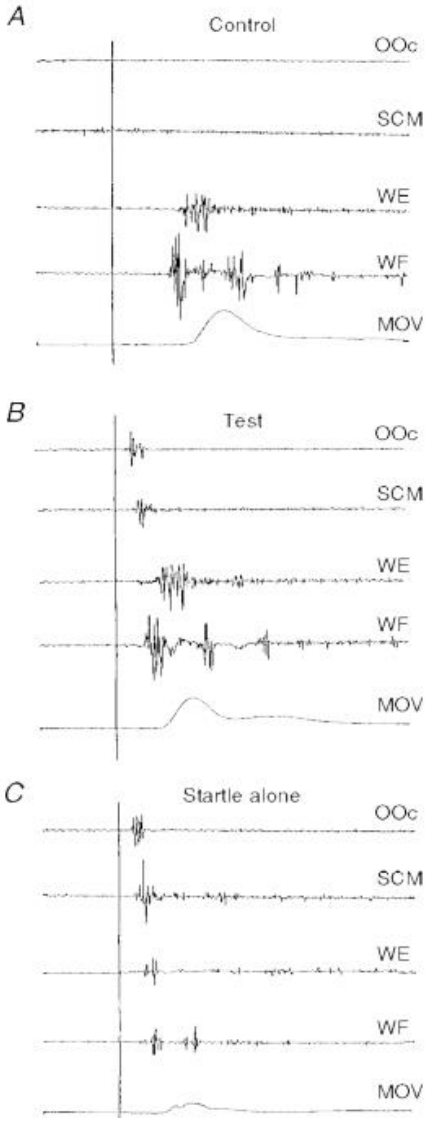

Figure 3. SR vs classic startle example. There is no EMG activity in SCM muscle during voluntary movement (top). There is a fast (<120 ms) EMG activation in SCM muscle during SR (middle) and classic startle (bottom) trials. [14]

There is some evidence that SR is mediated by the lower parts of the brain (i.e. reticular formation) [12], [14], [16]–[18]. SR movement and muscle activity onsets are between ~30 to ~130ms faster than the voluntary (non-SAS-elicited) onsets depending on the task [12], [14], [19], [20] (Figure 2). These studies suggested that, SR is too fast to be mediated by the corticospinal tract and the reason behind this faster onset is the involuntary release of the subcortically stored planned movement through reticulospinal tract by SAS. Alternatively, some studies argue that SR uses the same neural pathway as voluntary-initiated movements. They relate the faster reaction times to higher level of preparation during SAS trials. This theory was rejected with the studies that showed the SCM+ (SAS trials resulting to SR) trials have faster reaction time than SCM- trials (SAS trials with no SCM activity before 120ms, therefore no SR) while using the same loud sound [20], [21] and having the same preparedness [21]. However, the strongest

evidence in favor of the subcortical storage theory is the presence of SR in individuals with cortical damage. SR resulted in no differences in onset time of wrist flexion and ankle dorsiflexion tasks between individuals with pure hereditary spastic paraplegia (HSP with intact reticulospinal tracts) and control group, while the HSP group voluntary initiated movements were significantly slower than the control group. Presence of SR in these individuals implies the role of the reticulospinal tract in releasing a subcortically planned movement [22], [23]. In addition, individuals with different levels of stroke [17], [24], [25], and Parkinson [26], [27] showed the same faster SR movement initiation and intact SR.

1.1.3 SR in Stroke

In iwS, SR has been shown to elicit faster muscle activity and faster movement reaction in lower limbs during a balance test [24], and faster muscle activity onsets with more appropriate muscle activation in upper extremity movements [17], [25], [28]–[30]. Specifically, when elbow flexion movements of iwS are elicited via SR, the onset latency and agonist/antagonist timing of iwS are not statistically different from unimpaired subjects of the same age [17]. This result was replicated by an independent group [30], who additionally demonstrated that SR could be evoked using electrical stimulation in iwS. In addition to temporal characteristics, SR increased the amplitude of muscle activity, which is most striking in individuals with more severe impairment [25], [28]. Similar results (decreased onset latency and increased muscle activity) are seen during SR in hand extension/flexion tasks post-stroke, which indicates that SR can influence movement across the entire limb post-stroke [29].

1.1.4 Abnormal Flexion Activity

The abnormal flexor activity is a concerning element when using SR in iwS. IwS usually suffer from abnormal flexor activity, especially in individuals with more impairment. This abnormal activity (e.g. early flexion during an extension task) usually appears in elbow, wrist, and finger flexors to cause loss of independent joint control in individuals with chronic stroke [31]. It is important to mention that the abnormal flexor activity is different from spasticity. Individuals with damage to brain might experience spasticity and their spasticity would provoke tightened and shortened flexor muscles and hyperexcitable stretch reflexes [32]. The abnormal flexor activity in the elbow contributes to the impaired reaching movement in individuals with stroke [33] more than flexor spasticity. This abnormal flexor activity is likely

a result of increased reliance on the reticulospinal tract (which is the same pathway suggested for SR movements) in iwS [31], [34], [35]. Therefore, the abnormal flexor activity makes use of SR in iwS complicated and the capacity of SR to alter muscle activation and abnormal flexor activities has led to some arguments against the use of SR as a therapeutic intervention for iwS. Thus, three critical gaps in our knowledge need to be addressed before a clinical trial is appropriate.

1.2 Objectives and Hypothesis

SR has to be tested to make sure it is safe and has some improvement effects in iwS's movement and muscle activities, before performing long and numerous sessions of SR training studies on iwS population. The objective of this dissertation is evaluating SR as a therapy tool by addressing the following gaps in the literature:

1.2.1 Gap1

SR's capacity to change muscle activity during multi-jointed and more functionally relevant reaching movement has only been cursorily studied to date. Most previous upper extremity SR studies have evaluated single joint movement or movements restricted to 1 dimension [36], [37], [46], [38]–[45] including the previous studies on iwS [17], [24], [28]. In unimpaired individuals, SR readily evokes multi-jointed reaching movements [20], [47] and combined tasks such as simultaneous pinch and elbow flexion [48] in an unrestricted workspace. However, iwS have task-inappropriate muscle activity patterns and spasticity, which casts doubt on whether SR would be accessible during unrestricted point-to-point reaching movements post-stroke, and would generate quantitative changes that improve point-to-point reaching performance in this population. **Therefore, our first objective (Aim 1) is to evaluate the impact of SR during unrestricted, two-dimensional point-to-point reaching tasks in individuals with a wide range of impairment.** In chapter 2, the SR movements are compared to voluntary movements during reaching to three targets covering a large workspace in horizontal 2D surface. We will assess these movements in individuals with mild, moderate and severe stroke and their unimpaired arms. We hypothesize that (H1): SR would be present in iwS and lead to improvement in muscle activation and movement in individuals with severe/moderate impairment. SR would decrease reaction times, increase

muscle activation and EMG amplitude in all iwS, and it would produce larger reaching distances in individuals with severe/moderate impairment.

1.2.2 Gap 2

Single-jointed or one-dimensional movements are enhanced (faster onsets and larger EMG amplitude) during SR trials in iwS [17], [24], [28], but no one has evaluated the impact of SR on the voluntary-initiated activities after exposure to SR. We cannot be certain if SR is a practical therapeutic tool, unless training with SR can result in enhancement in voluntary-initiated movement (occurring without a startle or SAS), SR cannot be a practical therapeutic tool. In chapter 3, we investigate the first and last 10 voluntary-initiated (non-SAS) movements to each target for individuals with severe and moderate stroke to monitor the amount of alteration of movements and EMG activations. **Our second objective (Aim 2) is to evaluate the impact of exposure to SR on the voluntary execution of point-to-point reaching task performed in Aim 1.** Therefore, in chapter 3, we will measure and compare the parameters mentioned in Aim 1 over the voluntary-initiated trials. We hypothesize that (H2): a single session of SR reaching will enhance the range of motion and the accuracy of voluntary movement. We predict that exposure to SR would increase the movement distance and displacement and decrease the movement final error in individuals with severe/moderate stroke. We also predict that the EMG onset will decrease and EMG amplitude will increase following an SR session.

1.2.3 Gap 3

While SR appears to enhance movement in iwS, it is also interrupted by functionally inappropriate flexor activity disrupting movement to the intended target [18], [28], [49]. This inappropriate flexor activity is more pronounced in individuals with severe impairment and has been shown to be the largest in individuals with high spasticity [18]. The abnormal flexor activity during SR has been suggested to be the result of an unsuppressed classic startle response [28], [50]. Therefore, there is a concern about the impact of the abnormal flexor activities on aggravating the voluntary-initiated movement strategies in iwS. Muscle Synergy Analysis (MSA) is a deeper analysis than behavioral and clinical assessments for assessing the movement strategy changes in iwS. No study has evaluated the voluntary-initiated muscle synergies after exposing the iwS to SR. **Our objective (Aim 3) is to evaluate the muscle synergy of**

voluntary-initiated movements during the SR session for iwS with different level of impairments to investigate the impact of the abnormal flexor activity on voluntary-initiated trials. In chapter 4, we use the voluntary trials mentioned in chapter 3 from all the subjects. In addition, we collected the same data from an unimpaired age-match group using the exact same experiment mentioned in chapter 2 to use as control data. We hypothesize that (H3): the muscle synergies of the moderate and severe groups are different from the mild and control groups before exposure to SR; however, these muscle synergies get more similar to the control group after exposure to SR. It means that we expect the number of muscle synergies in individuals with severe and moderate stroke will increase during the session to reach the same number as individuals with mild stroke and unimpaired control group. We also hypothesize that there are abnormalities in the muscle synergies of individuals with moderate and severe impairment at the beginning of session. It means that the muscle synergy similarity indices to norm synergy for severe and moderate groups are lower than the rest of the groups at the beginning. However, we expect these abnormalities in moderate and severe individuals disappear after exposure to SR, i.e. their similarity indices will increase after exposure to SR.

1.2.4 Aims

To summarize, there are three gaps in our knowledge about SR: first, if SR will be effective in multi-joint movement; second, if SR leads to functional voluntary movement improvements and third if the abnormal flexor activities seen in previous studies impact the muscle synergies. We define the following aims in this dissertation to fill these gaps:

Aim 1: Investigating the capacity of SR to enhance multi-jointed point-to-point reaching post stroke.

Aim 2: Establish the extent to which SR enhances the voluntarily-initiated movement.

Aim 3: Investigating the capacity of SR exposure to alter quantitative muscle synergies of voluntarily-initiated movements in iwS.

CHAPTER 2

2 INVESTIGATING THE CAPACITY OF StartReact TO ENHANCE MULTI-JOINT POINT-TO-POINT REACHING POST STROKE.

The results of this chapter have been published under doi: 10.1007/s00221-020-05797-9. [25]

2.1 Abstract

Objective: StartReact elicits faster, larger, and more appropriate muscle activation in individuals with stroke but has been only cursorily studied to date during multi-jointed reaching. Our objective was to evaluate StartReact on unrestricted, two-dimensional point-to-point reaching tasks post-stroke.

Method: Data from 20 individuals with stroke was collected during point-to-point reaching. Voluntary and StartReact trials were compared among individuals with mild and severe/moderate stroke, and their unimpaired arm.

Results: An increase in muscle activation percentage, larger muscle activity amplitude and faster muscle activity onset were observed during StartReact trials. Despite changes in muscle activity, metrics of movement (distance, final error, linear deviation) were not different between StartReact and Voluntary trials except in severe/moderate stroke who had larger reaching distances during StartReact.

Conclusion: While StartReact impacted many metrics of muscle activity, the most profound effect was on muscle activation percentage increasing 34% compared to Voluntary which allowed severe/moderate subjects to increase reaching distance. The increase in distance did not translate to decrease in final error suggesting that the additional movement was not always directed towards the appropriate target.

Significance: These results indicate that StartReact has the capacity to activate paralyzed muscle in severe/moderate patients, but future studies are needed to explore the possible use of StartReact in the rehabilitation.

2.2 Introduction

The capacity of a startling stimulus to elicit voluntarily planned movements, a phenomenon referred to as StartReact (SR), has been investigated extensively for the past 20 years [14]. SR has been used as a tool to evaluate the underlying mechanisms of neurological diseases and injuries including stroke [17], [18], [24], [29], [30], [51], spinal cord injury [51], [52], Parkinson's [26], [27], corticospinal degeneration [23] and hereditary spastic paraplegia [22]. SR has been shown to elicit faster, larger, and more appropriate muscle activation in individuals who have had a stroke [17], [24], [28]–[30]. Specifically, when elbow flexion movements are elicited via SR, the onset latency and agonist/antagonist timing of iwS are not statistically different from unimpaired subjects of the same age [17]. This result was replicated by an independent group [30] who additionally demonstrated that SR could be evoked using electrical stimulation in individuals with stroke (iwS). In addition to temporal characteristics, SR increased the amplitude of muscle activity, which is most striking in individuals with more severe impairment [28]. Similar results (decreased onset latency and increased muscle activity) are seen during SR in hand extension/flexion tasks post-stroke indicating that SR can influence movement across the entire limb post-stroke [29].

The capacity of SR to alter muscle activation has led some to argue for the use of SR as a therapeutic intervention for iwS but SR's capacity to change muscle activity during multi-joint, more functionally relevant reaching movement has only been cursorily studied to date. Most previous SR work has evaluated single joint movement or movements restricted to 1 dimension [36], [37], [46], [38]–[45] including the previous work in iwS [17], [28]. In unimpaired individuals, SR readily evokes multi-jointed reaching movements [20], [47] and combined tasks such as simultaneous pinch and elbow flexion [48] in an unrestricted workspace. However, iwS have abnormal muscle activity patterns and spasticity, which casts doubt on if SR would be accessible during unrestricted reaching movements post-stroke and more relevantly generate quantitative changes that improve reaching performance in this population. Moreover, SR extension movements are interrupted by functionally inappropriate flexor activity disrupting movement to the intended target [18], [28], [49]. This inappropriate flexor activity is more pronounced in individuals with severe impairment and has been shown to be largest in individuals with high spasticity. These

abnormalities draw into question if SR would be effective, or even advisable, in individuals with severe/moderate stroke.

Therefore, the objective of this study is to evaluate the impact of SR during unrestricted, two-dimensional point-to-point reaching tasks in individuals with a wide range of impairment – particularly severe and moderate stroke. We hypothesized that (H1) SR would decrease reaction times, increase muscle activation and muscle amplitude in all iwS, and produce larger reaching distances in individuals with severe/moderate stroke.

2.3 Methods

2.3.1 Subjects

Twenty individuals (age = 19 to 85 years) with chronic severe-to-mild stroke (UEFM = 8-66/66) and no-to-severe spasticity (Modified Ashworth = 0-4/4) participated in this study (Table 1). Inclusion/exclusion criteria were: no injury to arm/shoulder in past 6 months, at least 6 months post-stroke, no hearing loss/sensitivity, no dizzy or fainting spells, no seizure or heart attacks, measurable impairment in the upper extremity, and could not be pregnant. This study was approved by Arizona State University's Institutional Review Board STUDY00002440. Subjects were informed of all potential risks prior to participation in the study and verbal/written consent was obtained.

Table 1. Summary of included subjects' characteristics

Number	Sex	Age (years)	Duration from onset of stroke (years)	Paretic arm	UEFM Score	Modified Ashworth Score			
						Shoulder flexion	**Shoulder extension**	**Elbow extension**	**Elbow flexion**
1	M	31	0.9	R	65	0	0	0	0
2	M	77	3.7	R	25	0	0	3	3
3	M	59	5.3	L	41	0	1	0	1+
4	M	36	10.4	*R>L	31	0	0	3	2
5	F	66	4.7	R	66	0	0	0	0
6	M	61	1.7	L	55	1	1	1+	0
7	F	61	1.6	L	64	0	0	0	0
8	M	47	1.5	L	61	0	0	0	0

9	F	39	3.7	R	19	3	3	3	3
10	M	51	1.1	L	24	0	1	3	3
11	M	28	0.5	R	35	0	0	2	2
12	M	52	11.7	L>R	58	0	0	0	2
13	M	71	12.4	L	8	1	1	3	4
14	F	65	17.4	R	65	0	0	0	0
15	F	49	1.2	L	11	1	0	2	2
16	F	65	7.8	L	11	0	1	1+	0
17	F	19	0.8	L>R	14	0	0	0	1
18	M	70	2.5	L	64	0	0	0	0
19	F	33	13.5	R	11	1	1	1	1
20	M	68	3.3	R	53	0	0	0	0

**R > L means both arms are impaired, but the right arm is more impaired, therefore, the UEFM and MA Scores are measured for the right arm.*

2.3.2 Protocol

Subjects were asked to sit comfortably in the experimental chair. Ag/Cl surface electrodes [MVAP Medical Supplies, Newbury Park, CA] were used to record activity from the brachioradialis (BR), biceps (BIC), triceps lateral head (TRI), pectoralis (PEC), anterior deltoid (AD), and posterior deltoid (PD) muscles. Electrodes were also placed on the left (LSCM) and right (RSCM) sternocleidomastoid muscles to monitor startle activity [53]. EMG signals were amplified by the Bortec AMT-8 system [Bortec Biomedical, Calgary, Alberta, Canada]. This system had a bandwidth of 10-1000Hz, an input impedance of 10GΩ, and a common mode rejection ratio of 115 dB at 60Hz. Electromyography (EMG) data were recorded at gain of 1500 and frequency of 3000Hz by a 32-channel, 16-bit data acquisition system [NI USB-6363, National Instrumentation, Austin, TX].

For this study, the InMotion2 Interactive Therapy System (Interactive Motion Technologies, Inc, Watertown, MA 02472 USA) was used to record time and position data for the reaching tasks performed by the subject at a sampling frequency of 1000 Hz. The InMotion2 system is a commercial version of the MIT-Manus and is designed for use in a clinical environment [54]. The arm rested on a custom-made arm support attached to the robot arm. Both the impaired and unimpaired arms were evaluated for all

subjects. Three subjects had a stroke in both arms. For these individuals, the most impaired arm was tested, and the least impaired arm was not included in analysis.

Subjects were instructed to perform reaching movements to three targets starting from an initial arm position of shoulder abduction at 70°, shoulder flexion at 40° and elbow angle at 90° (all ±5° to subjects comfort). A monitor in front of the subjects depicted location of the home and target positions as well as the location of their hand. The position of home circle was fixed. The distance between home and target circles was proportional to the subjects' arm lengths. This distance was calculated using the formula $R = \frac{\sin(70^o) \times length\ of\ upper\ arm + length\ of\ forearm}{5}$ (Figure 4).

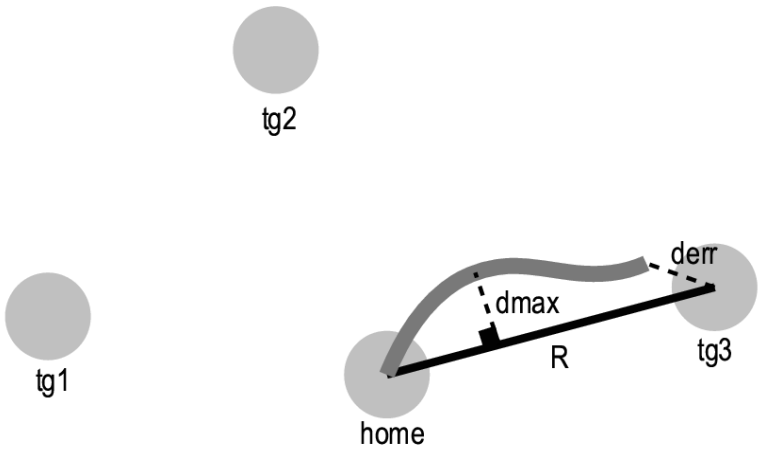

Figure 4. Target positions. The locations of target and home circles for the right arm are presented. The left arm targets were the mirror image of these targets. R was the distance between the home circle and the target circles (black line). The gray line is the movement trajectory from the start point to the end point. dmax is the maximum distance between the movement trajectory and the axis connecting the home to the target. derr is the distance between the target and the end point. tg: target.

Subjects were instructed to move following two soft (80 dB) auditory sounds. Subjects were told to plan to move after the first sound (GET READY) and reach as fast as possible after hearing the second sound (GO). GO cue was delivered between 2-3 seconds after the GET READY cue to prevent anticipation. The cursor disappeared right after they left the home circle and reappeared after 1 second. Subjects practiced reaching to each target 15 times before data collection. The cursor did not disappear during the practice time. There were two additional trial types: Classic startle and SAS trials. During these trials the GET READY cue (classic startle) or the GO cue (SAS) was replaced with a startling acoustic sound of 115dB, generated by Siren Speaker TS-333S, 12V DC/1000mA/122dB with 0.01s duration time

and 0.002s rise time. SCM activity was monitored to determine the presence of SR. Activity prior to 120ms (SCM+) was defined as SR and was included in further analysis.

Subjects performed nine blocks of arm reaches. Each block consisted of 15 reaches to a single target. The order of each block was randomly assigned. Each block contained two different trial types: 1) Voluntary (VOL): In 66.7% of trials GO and GET READY were at 80 dB; and 2) SAS trials: In 33.4% of trials GO was at 115dB. Additionally, the first block of each target contained a classic startle trial (a total of 3 for each arm) where the GET READY was 115dB. Modified Ashworth Scales and Upper Extremity Fugl-Meyer assessments (UEFM) were collected at the end of the experiment.

2.3.3 Data Analysis

EMG data were rectified and smoothed in MATLAB (R2017b) using a 10-point moving average. We calculated the following outcome measures: EMG onset, movement onset, movement distance, deviation from linearity, final error, mean muscle activity amplitude, and percentage of muscle activation. EMG onset was first detected using a custom MATLAB script that detected EMG activity greater than the background activity plus 3 standard deviations. Background was calculated using 500 ms prior to the GO cue. Visual inspection and corrections were conducted by an experimenter blinded to trial type. Movement onset was defined as the time when the subject left the 1 cm HOME circle. Movement distance was the distance travelled from the movement onset until the velocity of movement was found to be less than 0.0001 m/s (final position). We normalized the movement distance to R (Figure 4). Deviation from linearity was defined using the following formula $\frac{d_{max}}{R}$ [55]–[57]. Final error was the distance between the final position and the center of the intended TARGET. Mean muscle activity amplitude was calculated as the mean EMG activity over the first 70 ms proceeding the onset of muscle activity. EMG amplitude was normalized to the percent of maximum voluntary muscle activity collected during the experiment. The percentage of muscle activation for each muscle was calculated as the number of trials where an EMG onset could be identified divided by the total number of trials and multiplied by 100. Finally, we defined SCM+% as the number of SAS trials with SCM activity prior to 120ms divided by the total number of SAS trials for each subject.

Trials in which the subject failed to move or was distracted (e.g. coughed, yawned) were eliminated from analysis (4.8 % of trials). Additionally, 3 subjects were eliminated because we were not able to achieve at least 3 SR trials. Two subjects were withdrawn because they were uncomfortable with the experimental paradigm (fear of loud sound and chair was uncomfortable). The final subject was not able to perform the task i.e. did not plan movement for VOL or SR trials.

2.3.4 Statistical Analysis

Individuals with stroke were separated into two groups: 11 severe/moderate (UEFM < 45/66) and 9 mild (UEFM > 45/66). The unimpaired arm (of 17 subjects; 3 subjects had bilateral stroke) was evaluated for comparison. We used a Generalized Linear Mixed Model (GLMM) [58] in R 2017 version 3.4.2 [59] which assumes Gaussian (normal) distribution for all the comparisons. Dependent variables included all calculated metrics listed above (e.g. onset latency, movement onset, etc.). The fixed effects were condition (VOL, SR), population (unimpaired, mild, severe/moderate) and muscle (BR, BIC, TRI, PEC, AD, PD). Subject was treated as a random factor and 95% confidence was used to define statistical significance. Furthermore, we used a one-way analysis of variance (ANOVA) to examine the effect of population on SCM+%.

2.4 Results

The SCM activity prior to 120ms (SR trials) was observed in all the subjects in Table 1. 60.31 ± 6.60 %, 50.02 ± 69.64 % and 41.56 ± 5.52 % of the SAS trials in severe/moderate, mild and unimpaired arm groups were SR trials. The SCM+ percentages were not statistically different ($P > 0.36$) among the groups.

SR and VOL movements appeared mostly unaffected in unimpaired and mild, but in severe subjects SR movements were larger and recruited more muscles (Figure 5). Similar to results of younger adults [20], SR and VOL movement trajectories were not different (except onset latency) in the unimpaired and mild stroke groups (Figure 5a and 5b). Typical of SR, muscle activity was faster with similar activation patterns for both unimpaired and mild. Further, the SR amplitude of muscle activity was larger in unimpaired and mild stroke.

In severe stroke, SR had a larger impact on movement trajectory compared to mild and unimpaired groups (Figure 5c). During VOL, the representative severe subject #18 was unable to leave the HOME target and muscle activity was absent or significantly delayed. Conversely, SR movements left the HOME target and traveled away from the body at some point. Similarly, muscle activity, absent during VOL, was present in all muscles at a fast latency during SR. It is important to note that traces seen in figure 5c represent SR movement trajectories to all three targets. Thus, while SR movements were larger and directed away from the body, subjects often did not achieve the target, which matches the results from final error and deviation from linearity. (i.e. not different final error and larger deviation from linearity (Figure 7c and 7d).

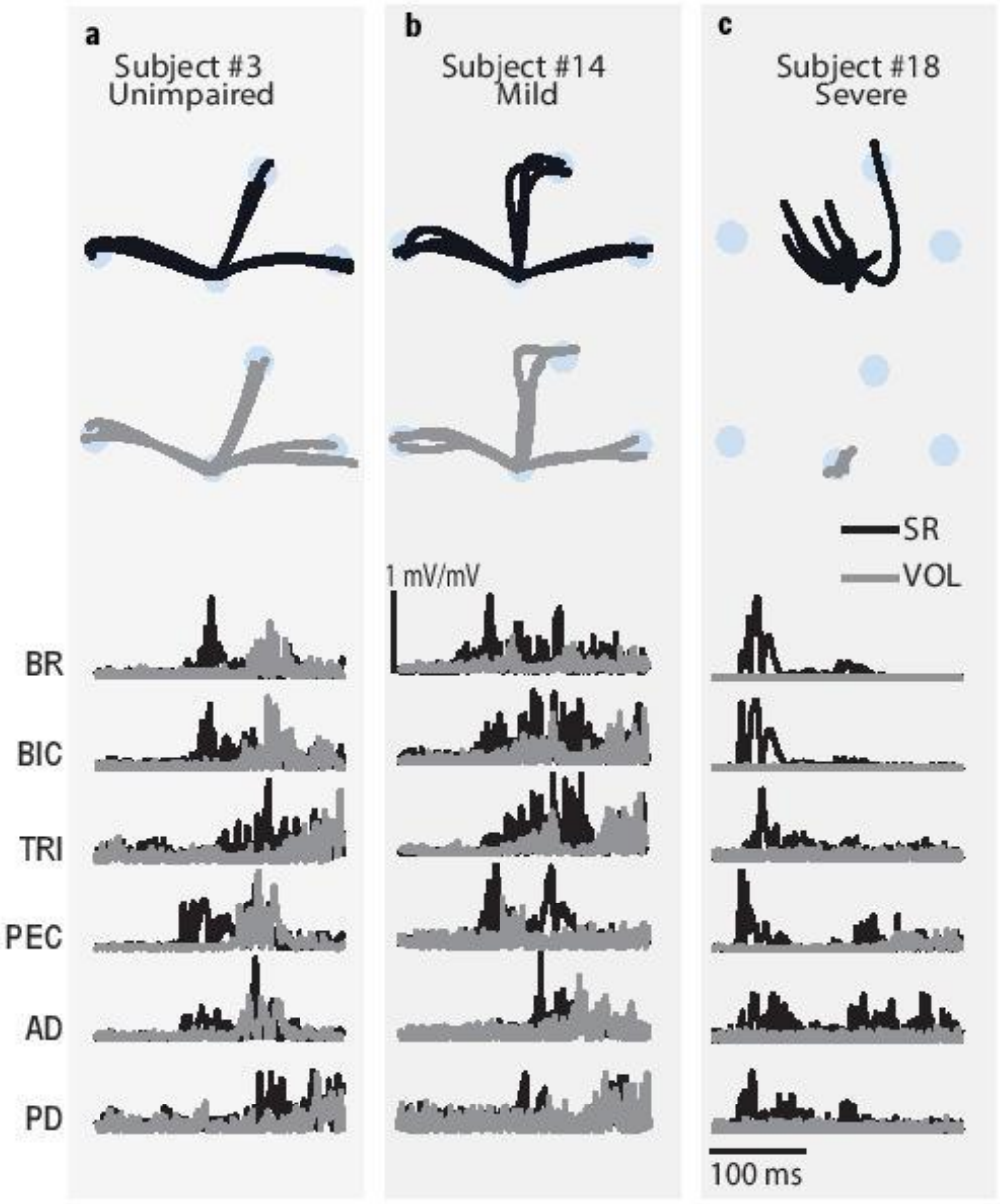

Figure 5. Representative movement trajectory and EMG data. VOL (gray) and SR (black) movement trajectories and EMG are depicted for individuals with unimpaired arm (a), mild (b) and severe (c) stroke.

Group results showed that SR trials had an increase in percentage of muscle activation (severe/moderate & mild), larger muscle activity amplitude (all groups) and faster muscle activity onset (all groups) (Figure 6). The percentage of muscle activation in all muscles (BR, BIC, TRI, PEC, AD, PD) in severe/moderate group was increased in SR trials ($avg\ \Delta = 0.34 \pm 0.057$, all: $P < 0.0001$). Percentage of muscle activation was also increased for some muscles in mild group during SR trials

($avg\ \Delta \text{ for BR, BIC and PEC} = 0.12 \pm 0.06$, all: P < 0.05) but not for TRI, AD and PD (all: P > 0.057). As expected, the percentage of activation during SR trials was not different from VOL in the unimpaired arm (all: P > 0.059), as indicated by the 96.83% average activation rate across all during the VOL condition. SR EMG amplitudes were larger for all populations (severe/moderate: $avg\ \Delta = 1.26 \pm 0.34\ mV/mV$, mild: $avg\ \Delta = 0.21 \pm 0.038\ mV/mV$, unimpaired: $avg\ \Delta = 0.22 \pm 0.029\ mV/mV$, all: P ~ 0). It is of note that during SR EMG amplitudes were greater than the maximum voluntary EMG activity in four muscles (BR, BIC, PEC, and AD) in the severe/moderate group. Typical of SR, SR EMG onset latencies were also faster than VOL for all populations (severe/moderate: $avg\ \Delta = 324.74 \pm 13.33\ ms$, mild: $avg\ \Delta = 128.45 \pm 11.21\ ms$, unimpaired: $avg\ \Delta = 99.55 \pm 6.20\ ms$, all: P ~ 0).

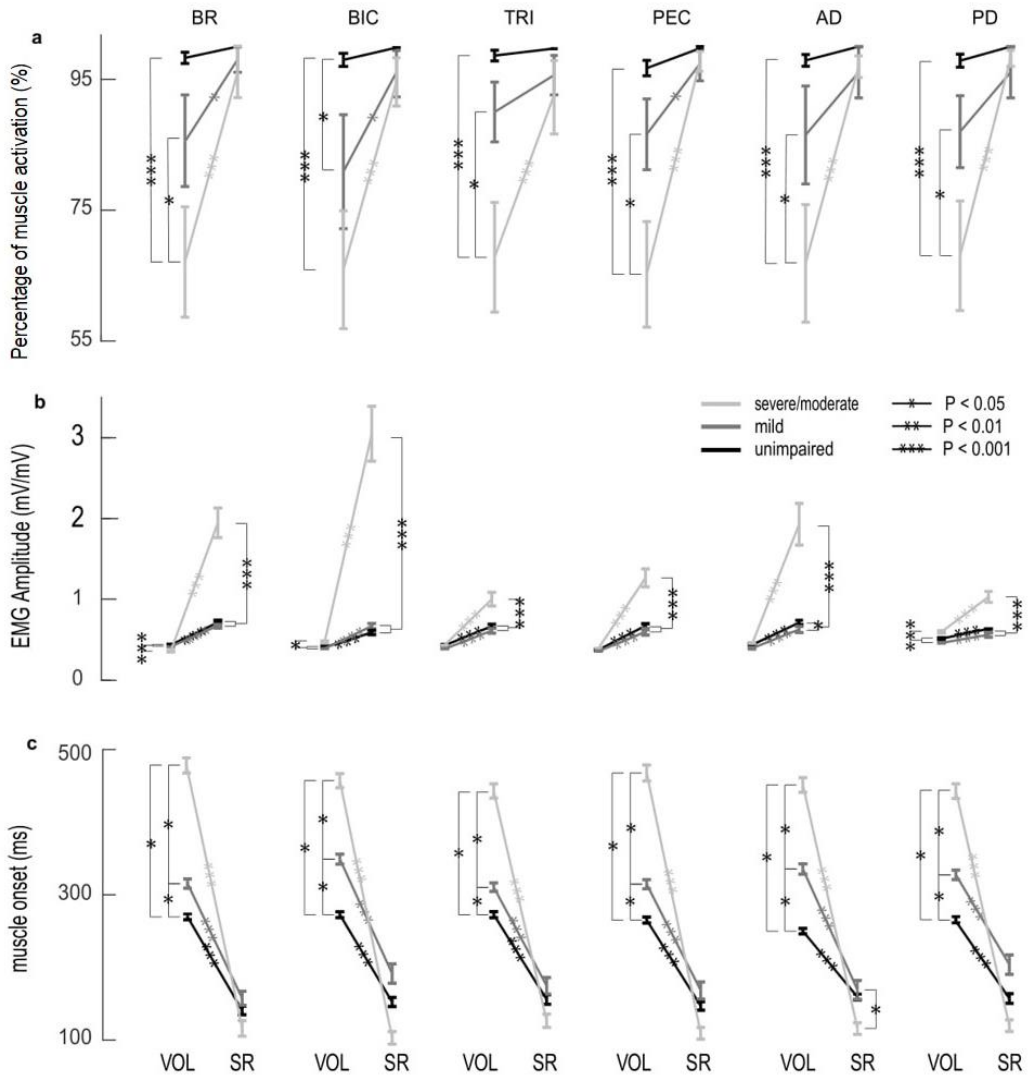

Figure 6. Group results of muscle activity metrics. The percentage of muscle activation (a), EMG amplitude (b), and EMG onset (c) are compared across populations: unimpaired, mild, severe/moderate.

Despite changes in muscle activity, metrics of movement (distance, final error, linear deviation) were largely not different between SR and VOL trials, (Figure 7) except in severe/moderate stroke who had larger reaching distances ($\Delta = 0.074 \pm 0.0023$ mm/mm, P = 0.001) and more deviation from linearity ($\Delta = 0.035 \pm 0.019\, ms$, P = 0.048). Final error was not different between SR and VOL trials across all populations (all: P > 0.15) and deviation from linearity was not different in unimpaired and mild groups (all: P >0.10). Movement distance was also not different for unimpaired (P = 0.11) and mild (P = 0.13).

Consistent with SR, movement reaction time was faster for all populations (severe/moderate: $\Delta = 190.17 \pm 9.34\, ms$, mild: $\Delta = 111.25 \pm 6.33\, ms$ and unimpaired: $\Delta = 78.23 \pm 8.63\, ms$, all: P ~ 0).

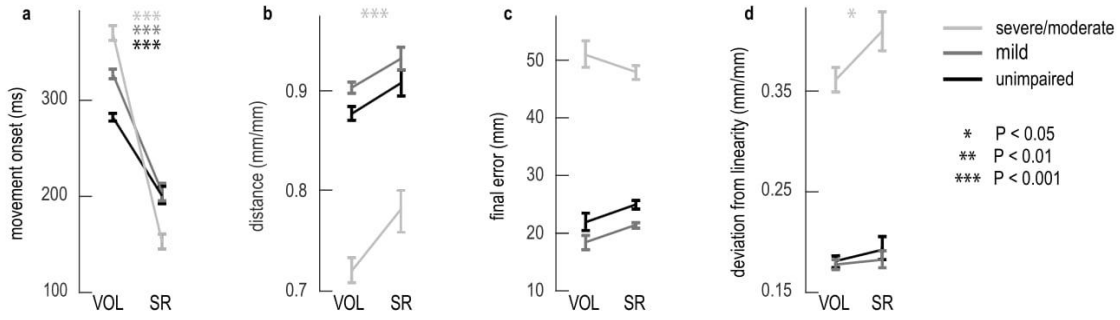

Figure 7. Group results of movement metrics. Movement onset (a), normalized distance traveled (b), final position error (c), and deviation from linearity (d) during VOL and SR are compared within each population: unimpaired, mild, and severe/moderate.

While VOL trials were different across the populations in terms of percentage of muscle activation and onset latency, these metrics were not different across populations during SR trials. During VOL, the percentage of muscle activation was smaller in the severe/moderate group compared to both mild ($avg\ \Delta = 0.20 \pm 0.09, all\ P < 0.03$, except for BIC P = 0.072) and unimpaired ($avg\ \Delta = 0.31 \pm 0.09$, P < 0.0001) but during SR trials, the percentage of muscle activation was not different across all of the groups (all: P > 0.2). Similarly, VOL EMG onset in the unimpaired group was faster than mild ($avg\ \Delta = 42.03 \pm 6.37 ms$, P < 0.041) and faster than severe/moderate ($avg\ \Delta = 245.29 \pm 10.19\, ms$, P < 0.025) but during SR trials there was no difference in EMG onset across all the groups (all: P > 0.11) except for AD which had a faster onset in the severe/moderate group ($\Delta = 38.02 \pm 11.41\, ms$, P < 0.01). Finally, unlike the previous metrics, SR EMG amplitudes were larger in severe/moderate compared to mild ($avg\ \Delta = 1.00 \pm 0.17, all: \mathrm{P} < 0.001$) and unimpaired ($avg\ \Delta = 1.03 \pm 0.18, all: P < 0.001$).

In the severe/moderate group, flexor onset latencies were faster than extensors onset during SR. Specifically, flexor (BIC, PEC,AD) onset latencies were faster than the extensor TRI ($avg\ \Delta = 24.60 \pm 10.52\, ms$, all: P < 0.045). Further, flexor (BIC, PEC) onset latencies were also faster than the extensor PD ($avg\ \Delta = 30.77 \pm 10.56\, ms$, all: P < 0.020). Moreover, EMG amplitude of BIC is ~3 times and EMG amplitude of BR and PEC are ~2 times of maximum voluntary EMG amplitude.

Finally, classic startle resulted in no movement or muscle activity in the mild and unimpaired but 45% of the severe/moderate group showed movement – always directed towards the body. No movement or muscle activity was reported for classic startle in unimpaired arms or mild impaired arms (all traces from all subjects depicted, Figure 8a and 8b); however, 5 out of 11 severe/moderate subjects moved out of the HOME circle during classic startle and generated muscle activity during 93% of trials. All classic startle movements were directed towards the body (Figure 8c).

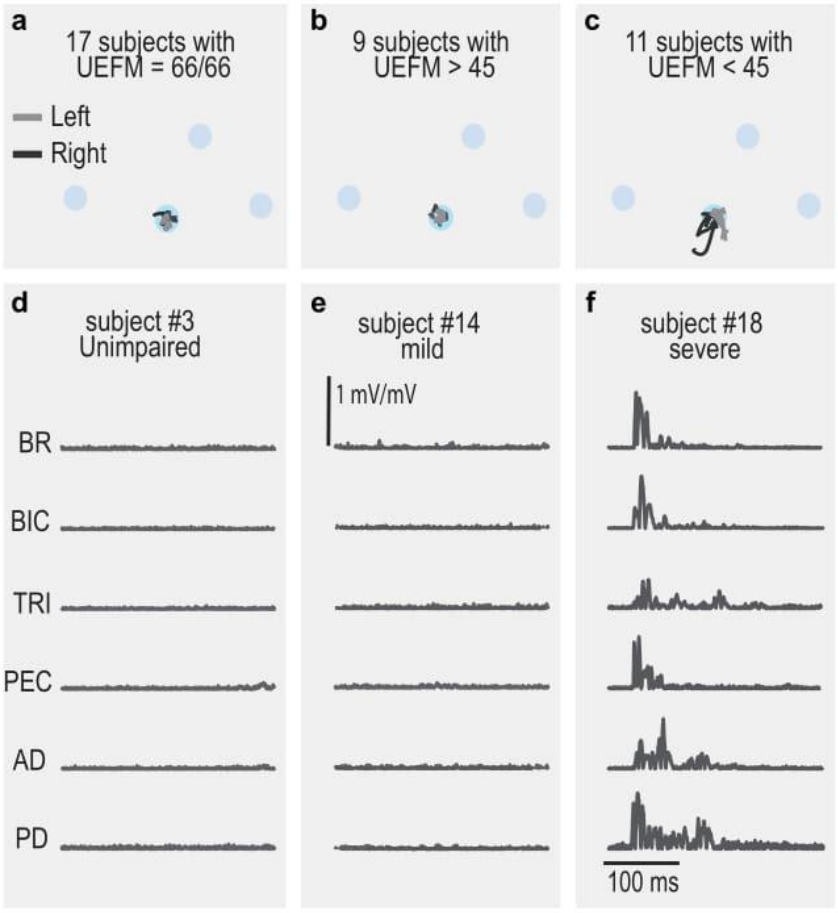

Figure 8. Classic startle data. All movement trajectories recorded during classic startle trials are depicted for unimpaired (a), mild (b), and severe/moderate (c) groups. In contrast, representative EMG from a single classic startle trials for each population is presented.

2.5 Discussion

2.5.1 Summary

The objective of this study was to evaluate the impact of SR on unrestricted, two-dimensional reaching tasks in individuals with a wide range of impairment – in particular severe and moderate stroke. SR was robustly present in subjects across all impairment levels. Similar to prior reports in unimpaired adults [20] VOL and SR trials were nearly not different in terms of percentage of muscle activation and movement metrics in the mild and unimpaired groups; however SR had a significant effect on muscle activity in the severe/moderate group. All EMG metrics enhanced such as larger muscle activity and decreased muscle latency, but SR had the most profound effect on the percentage of muscle activity. During VOL, the severe/moderate group activated their muscles during only 62.44% of trials compared to 97.85% during SR trials. This additional muscle activity allowed severe/moderate subjects to increase reaching distance but did not translate to a decrease in final error suggesting that the additional movement was not always directed towards the appropriate target. In conclusion, these results indicate that SR allowed the activation of paralyzed muscle in severe/moderate patients allowing further reaching but has little impact on mild patients during point-to-point reaching.

2.5.2 SR and Rehabilitation

To our knowledge, SR in the upper extremity has only been evaluated in 28 iwS total. This study nearly doubles the number of subjects evaluated to date to 51 and is the first SR study to include individuals with bilateral stroke. SR was robustly present in most (87%) of the iwS in this study (Upper Extremity Fugl-Meyer's ranging 8 - 66 and Modified Ashworth scores ranging: 0 - 4) and was well tolerated i.e. no adverse reactions or negative feedback were reported. It is of note that SR is also occasionally absent in young, neurological intact individuals [20], [60]; thus it is uncertain if the absence of SR is related to the stroke or just a naturally occurring phenomenon.

The most profound impact of SR was the increase in percentage of muscle activation, and the amplitude of that activation, in the severe/moderate stroke group. SR increased the percentage of muscle activation 34% and increased activation amplitude to nearly two times the maximum voluntary capacity of

the individual in 66% of muscles, suggesting SR is a profound way to activate paralyzed muscle. This impact was immediate – occurring in a single session and required no training. Furthermore, the increased muscle activity allowed severe/moderate individuals to generate larger reaching movements. There are several studies showing that SR can often increase EMG amplitude [48], [53], [61] and provocatively allow participants to generate forces larger than maximum voluntary contractions [62] in individuals without stroke. This study indicates that this phenomenon is present in individuals with stroke which may facilitate training, in particular for individuals with severe stroke.

Still it is important to note that the final error was not altered suggesting reaching movements were not necessarily functional. The lack of improvement in final error may result from a shift from reflexive to voluntary control during the time course of the SR response. It has been demonstrated that when SR is applied to tasks requiring high endpoint accuracy, SR movements are initiated quickly but to accommodate the increased constraints, subjects slow down to achieve higher accuracy [39]. This indicates a likely change in neural mechanisms governing the response which may limit the capacity of SR to be a rehabilitation tool during tasks of increased precision. Still, this study evaluated a single SR session (~1 hour) with only 45 SR trials per arm. A larger dose of SR over the course of several days may be required to see significant changes to target acquisition. In individuals with mild stroke, SR increased the amplitude of muscle activity, but no other metrics of movement were altered. This indicates that either SR was not an appropriate target for individuals with mild stroke or that SR did not generate quantitative improvements in tasks that were already readily performed by the subject. Before exploring SR as a therapeutic target, it is important to assess the potential risk to severe patients. It has been noted in different studies that SR generates abnormal and inappropriate flexor activity that disrupts movement [18], [28], [49]. Further, this activity increases with impairment. This raises concerns that more extended sessions of SR stimulation might induce neuroplastic changes that could further excite flexor synergies or spasticity. An alternative hypothesis is that SR might allow release spasticity through endogenous stimulation of paralyzed muscle. One of our most effective therapies to release spasticity is functional electrical stimulation (FES) of spastic muscle [63]. This works by releasing microfilament bridges and allowing the influx of ions to the muscle. SR might allow an endogenous stimulation of muscle which

could potentially release muscle activity. Still, neither of these hypotheses has been explored and further evaluation is needed to determine whether SR is a safe and effective method to treat neurological impairment and spasticity following stroke.

2.5.3 Abnormal Flexor Activity

This work adds to the growing evidence that SR generates task-inappropriate flexor activation, particularly in individuals with severe stroke. Previous studies have shown that SR extension movements are interrupted by abnormal flexor activity that arrives at the beginning of movement. This activity pulls the subject away from the intended target (Honeycutt and Perreault 2012) and increases with impairment level (Honeycutt and Perreault 2014). Similarly, the abnormal activity in the flexors is larger in patients with severe spasticity [18]. In this report, SR EMG amplitude was larger than the maximum voluntary EMG in flexor (BR, BIC, PEC, and AD) but not extensor (TRI, PD) muscles in the severe/moderate group. Further in the severe/moderate group but not the mild group, the EMG onset of the flexors (BIC, PEC) was faster than the extensors (TRI, PD) highlighting the presence of abnormal flexor activity in our subject population as well. It has been suggested that this early flexor activity is the result of a hypermetric classic startle response [17], [18], [28]. However, it is important to note that the muscle activity during SR movements was not entirely the result of the classic startle response. Classic startle trials never resulted in movement directed towards the target compared to SR trials where extensor muscle activity was present allowing movement directed toward the targets. Taken together, these results indicate that SR in severe/moderate subjects was distinct from the classic startle response. Still, task-inappropriate flexor activity was present, disrupting movements particularly in the severe/moderate population which raises concerns about the use of this technique in rehabilitation.

2.5.4 Conclusion

The objective of this study was to evaluate the impact of SR on unrestricted, two-dimensional reaching tasks in individuals with a wide range of impairment – in particular, severe and moderate stroke. SR was robustly present in subjects across all impairment levels, but the most profound impact of SR was the increase in percentage of muscle activation, and the amplitude of that activation, in the

severe/moderate stroke group which led to increased reaching distance. This effect was immediate and required no training. Still enthusiasm is tempered because though SR increased reaching distance and muscle activity, the final error was not decreased which indicates that reaching movements were not necessarily functional. Future studies should evaluate the impact of longer-term SR exposure on both benefits of SR (increased percentage of muscle activity) as well as any potential safety concerns (increased flexion synergies).

CHAPTER 3

3 ESTABLISH THE EXTENT TO WHICH STARTREACT ENHANCES THE VOLUNTARILY-INITIATED MOVEMENT.

3.1 Abstract

Background: When movements of individuals with stroke (iwS) are elicited by startling acoustic sound, reaching movements are faster, further, and directed away from the body. However, these startle-evoked movements (StartReact) also elicit task-inappropriate flexor activity, raising concerns that chronic exposure to StartReact might induce heightened spasticity in the flexors during voluntarily-elicited movement.

Objective: The objective of this study is to evaluate the impact of StartReact exposure on voluntary movements during point-to-point reaching in individuals with moderate and severe strokes. We hypothesize that exposure to StartReact will increase task-inappropriate flexor activity which will negatively impact voluntarily-initiated reaching movement. Specifically, we expect an increase in task-inappropriate EMG activity in the flexor muscles (BR, BIC, PEC and AD) which will be associated with worse voluntarily initiated reaching performance (e.g. decreased distance and displacement and increased final error).

Methods: Eleven individuals with moderate-to-severe stroke (UEFM = 8–41/66 and MAS = 0-4/4) performed a voluntary point-to-point reaching during StartReact exposure.

Results: Conversely to our hypothesis, exposure to StartReact did not increase abnormal flexion but rather antagonist activity in the elbow flexors and shoulder horizontal adductors decreased, suggesting that abnormal flexor/extensor co-contraction was reduced. This reduction of flexion led to increased reaching distance (18.2% farther), movement onset (8.6% faster), and final accuracy (16.1% more accurate).

Conclusions: This study offers the first evidence that exposure to StartReact in iwS does not negatively impact voluntary movement; moreover, exposure may improve volitionally-activated reaching movements by decreasing abnormal flexion activity.

3.2 Introduction

When paired with a task goal, a loud, startling sound can result in enhanced movement parameters for individuals with stroke (iwS) [17], [20], [24], [25], [29], [65]. Specifically, previous studies showed that startle-elicited reaching movements preceded by a Startling Acoustic Stimulus (SAS) [13], [22], [25], [34], [66]–[69] are significantly faster [22], [25], [28], [69] and further [16], [20], [25], [39]. Startle-evoked hand extension in iwS also results in faster and larger muscle activity[29]. This phenomena is known as StartReact (SR) effect.

While provocative, there are several confounding factors that lead to diminished enthusiasm for this novel implementation. First, SR movements in iwS are interrupted by functionally inappropriate activation of the flexors during extension that increases with impairment and spasticity levels [17], [25], [28]. Specifically, when SR is used to initiate movement, heightened coactivation of antagonist flexor muscles interrupts agonist extensor muscles (e.g. triceps) leading to higher errors during point-to-point reaching tasks. The high error rate despite larger reaching movement indicates that reaching movements are not always directed towards the intended target [25], [39]. Some have argued this abnormal coupling is the result of increased reliance on brainstem structures [31], [35], [70]. If true, long-term exposure to SR may induce plastic changes that could lead to increased abnormal flexor activity during voluntarily-initiated movement. IwS are already afflicted with abnormal flexor synergies that significantly degrade movement [71], [72]. Thus, it is unclear if SR is a viable, or even advisable, rehabilitation tool. Further, previous work has only evaluated SR movement [13], [17], [20], [60], [70], [73]. No one has evaluated the impact of SR exposure on *voluntarily*-elicited movement. Due to safety concerns, before proceeding to a randomized control trial evaluating training effects, it is prudent to perform a preliminary analysis to determine if exposure to SR has a maladaptive effect on voluntary movement leading to task-inappropriate flexor synergies.

The objective of this study is to evaluate the impact of exposure to SR on voluntary movements (non-startle-evoked) during point-to-point reaching in individuals with moderate and severe stroke. Specifically, we evaluate voluntary initiated muscle activity, reaching distance, movement displacement,

movement onset, deviation from linearity, and final accuracy of reaching movements. We hypothesize that exposure to SR will increase task-inappropriate flexor activity, which will negatively impact voluntarily-initiated reaching movement. We expect an increase in task-inappropriate EMG activity in the flexor muscles (BR, BIC, PEC and AD) which will be associated with worse voluntarily initiated reaching performance (e.g. decreased distance and displacement and increased final error).

3.3 Methods

3.3.1 Subjects

Eleven individuals (age = 48 ± 19 years) with chronic severe to moderate stroke (Upper Extremity Fugl-Meyer = 8-41/66) and no-to-severe spasticity (Modified Ashworth = 0-4/4) participated in this study (Table 1). Inclusion/exclusion criteria included no injury to arm/shoulder in the past 6 months, at least 6 months post-stroke, no hearing loss/sensitivity, no dizzy or fainting spells, no seizure or heart attacks, measurable impairment in the upper extremity, and could not be pregnant. This study was approved by Arizona State University's Institutional Review Board STUDY00002440. Subjects were informed of potential risks prior to participation in the study and verbal/written consent was obtained.

Table 2. Summary of subjects' characteristics

Number	**Sex**	**Age (years)**	**Duration of stroke (years)**	**Paretic arm**	**UEFM* Score**	**Modified Ashworth Score**			
						Shoulder flexion	Shoulder extension	Elbow extension	Elbow flexion
1	M	77	3.7	R	25	0	0	3	3
2	M	59	5.3	L	41	0	1	0	1+
3	M	36	10.4	R>L**	31	0	0	3	2
4	F	39	3.7	R	19	3	3	3	3
5	M	51	1.1	L	24	0	1	3	3
6	M	28	0.5	R	35	0	0	2	2
7	M	71	12.4	L	8	1	1	3	4
8	F	49	1.2	L	11	1	0	2	2
9	F	65	7.8	L	11	0	1	1+	0
10	F	19	0.8	L>R	14	0	0	0	1

11	F	33	13.5	R	11	1	1	1	1

*UEFM: Upper Extremity Fugl-Meyer, **R > L means both arms are impaired, but the right arm is more impaired, therefore, the UEFM and Modified Ashworth Scales are measured for the right arm.

3.3.2 Protocol

Ag/Cl surface electrodes [MVAP Medical Supplies, Newbury Park, CA] were used to record activity from the brachioradialis (BR), biceps (BIC), triceps lateral head (TRI), pectoralis (PEC), anterior deltoid (AD), and posterior deltoid (PD), left (LSCM) and right (RSCM) sternocleidomastoid muscles. EMG signals were amplified by the Bortec AMT-8 system [Bortec Biomedical, Calgary, Alberta, Canada]. This system has a bandwidth of 10-1000Hz, an input impedance of 10GΩ, and a common mode rejection ratio of 115 dB at 60Hz. Electromyography (EMG) data were recorded at gain of 1500 and frequency of 3000Hz by a 32-channel, 16-bit data acquisition system [NI USB-6363, National Instrumentation, Austin, TX].

For this study, an InMotion2 Interactive Therapy System (Interactive Motion Technologies, Inc, Watertown, MA 02472 USA) was used to record time and position data for the point-to-point reaching tasks performed by the subject at a sampling frequency of 1000 Hz. The InMotion2 system is a commercial version of the MIT-Manus and is designed for use in a clinical environment [54]. Subjects' arms rested on a custom-made arm support which was attached to the robot arm and had minimum friction with the table.

Subjects were asked to do a point-to-point reaching task. Subjects sat comfortably in the experimental chair with an initial arm position of shoulder abduction at 70°, shoulder flexion at 40°, and elbow angle at 90° (all ±5° to subjects comfort). They were instructed to perform point-to-point reaching movements to three target circles starting from a fixed home position. Targets were designed to cover the workspace and include mostly shoulder horizontal adduction (Target 1), mostly elbow extension (Target 3), and combination of shoulder and elbow movement (Target 2) (Figure 9). Home and target circles were displayed on a monitor, with a cursor mapping the online location of their hand as visual feedback. The distance between home and target circles was proportional to the subjects' arm lengths. This distance

was calculated using the following formula for each subject: $R = \frac{\sin(70^{O}) \times length\ of\ upper\ arm + length\ of\ forearm}{5}$.

Reach targets were an average of 11.06 ± 0.25cm.

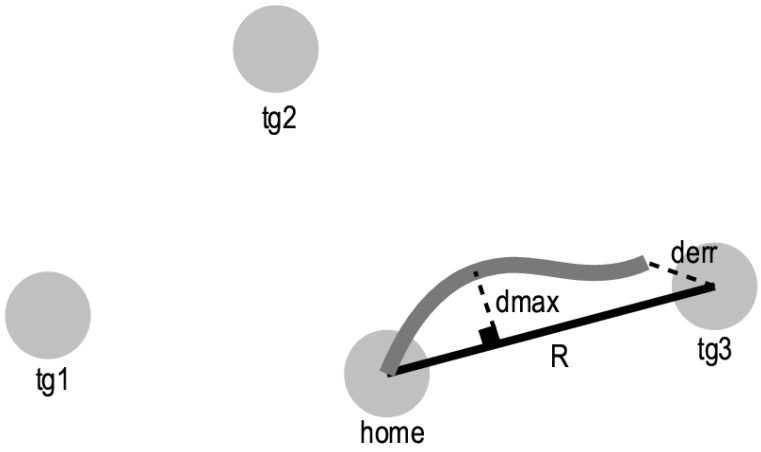

Figure 9. Target Positions. The locations of target and home circles for the right arm are presented. The left arm targets were the mirror image of these targets. R was the distance between the home circle and the target circles (black line). The gray line is the movement trajectory from the start point to the end point. dmax is the maximum distance between the movement trajectory and the axis connecting the home to the target. derr is the distance between the target and the end point. tg: target.

Subjects were asked to move following two soft (80 dB) auditory sounds. The instruction was to plan to move after the first sound (GET READY) and reach as fast and accurately as possible after hearing the second sound (GO). GO cues were delivered between 2-3 seconds after the GET READY cues to prevent anticipation. Prior to the main session, subjects practiced reaching from the fixed home position to the 3 position targets (15 times to each target) with visual feedback to make sure they learned the instruction. These trials were not included in the analysis.

Following practice, the online visual feedback of the cursor was removed. The cursor disappeared as soon as subjects left the home circle and reappeared half a second after they stopped in order to give subjects visual final point accuracy feedback. Subjects performed 135 reaches separated into blocks of 15 reaches to a single target. The order of blocks was randomized. This resulted in 45 reaches to each target. SAS was randomly applied during 1/3 of trials by replacing the soft GO cue with a startling sound of 115dB. The SAS was generated by Siren Speaker TS-333S, 12V DC/1000mA/122dB with a duration of 0.01 s and rise time of 0.002s. R/LSCM EMG activity prior to 120ms during SAS trials was defined as presence of SR [15], [74]. SAS trials were not further evaluated in this study but have been previously

reported [25]. Modified Ashworth Scales (MAS) and Upper Extremity Fugl-Meyer assessments (UEFM) were collected at the end of the session.

3.3.3 Data Analysis

The first 10 (beginning) and last 10 (end) voluntary trials to each target (i.e. the beginning and end of the session) were evaluated. EMG data were rectified and smoothed in MATLAB (R2017b) using a 10-point moving average. The following outcome measures were calculated: EMG onset, movement onset, movement distance, movement displacement, deviation from linearity, final error and EMG amplitude. EMG onset was first detected using a custom MATLAB script that detected EMG activity greater than the background activity plus 3 standard deviations. Background was calculated using 500ms prior to the GO cue. Visual inspection and corrections were conducted by an experimenter blinded to trial type. Movement onset was defined as the time when the subject left the 1cm HOME circle. The final point was the position that the velocity dropped down to 0.0001 m/s threshold. Movement distance was the distance traveled from the home position until the final point. The movement displacement is the absolute value of how far the final point is from the home circle. dmax was the maximum distance between the movement trajectory and the axis connecting the home to the target (Figure 9). Deviation from linearity was defined using the following formula $\frac{d_{max}}{R}$ [74]. Final error was the distance between the final point and the center of the intended target. EMG amplitude was calculated as the maximum EMG activity over the first 70ms preceding the onset of muscle activity. Finally, SCM+% was defined as the percentage of the SAS trials with right or left SCM activity prior to 120ms and calculated using the following formula: $100 \times \frac{number\ of\ SCM+\ trials}{number\ of\ SAS\ trials}$. Trials in which the subject was distracted and moved too late (no movement before 800ms) were eliminated from analysis (5.2% of trials).

3.3.4 Statistical Analysis

We hypothesized that exposure to SR would increase inappropriate flexor activity (faster and larger EMG flexor activities) which would negatively impact reaching movement (smaller distance, displacement and larger final error and slower movement onset). We used a Generalized Linear Mixed

Effects model in R 2017 version 3.4.2 [59] for all comparisons. Dependent variables included all outcome variables listed above (e.g. EMG onset, movement distance, etc.). The fixed effects were timepoint (beginning, end), target (Target 1, Target 2, Target 3), and muscle (BR, BIC, TRI, PEC, AD, PD). Subject was treated as a random factor and $P < 0.05$ was considered as statistical significance.

3.4 Results

Voluntary trials showed increased distance and displacement, reduced movement onset, and decreased final error at the end of the session. Additionally, muscle activity amplitude during voluntary trials did not change for most of the muscles during the session. SR trials, defined as the presence of SCM activity prior to 120ms after the GO cue (SCM+%), was present during an average of 60.3 ± 8.8% of the SAS trials.

At the end of the main session, subjects generated larger reaching movements towards the appropriate target (Figure 10). Three representative subjects (Figure 10) with varying levels of impairment and spasticity showed larger reaching distances at the end (black) compared to the beginning (gray) of the session. On average, at the end of the session, subjects generated voluntary reaches with 16.1% higher accuracy, 18.2% farther distance, 15.9% larger displacement, and 8.6% faster onset (faster onsets only present for Targets 1 and 2).

Group results showed that final error was affected by timepoint ($F_{1,549} = 21.25$, $P < 0.0001$) and target ($F_{2,549} = 19.13$, $P<0.0001$) leading to an average decrease of 0.83 ± 0.31cm (Target 1: 0.86 ± 0.28cm, $P = 0.0019$, Target 2: 0.99 ± 0.24cm, $P = 0.0017$, Target 3: 0.64 ± 0.31cm, $P = 0.013$) during the session (Figure 11.b). Distance was affected by timepoint ($F_{1,549} = 32.20$, $P < 0.0001$) and by target ($F_{2,549} = 47.66$, $P < 0.0001$) leading to an average increase of 1.93 ± 0.63cm (Target 1: 2.38 ± 0.50cm, $P = 0.0001$, Target 2: 1.24 ± 0.53cm, $P = 0.019$, Target 3: 2.18 ± 0.63cm, $P = 0.0006$) by the end of the session (Figure 11.c). Displacement was similarly affected by timepoint ($F_{1,549} = 41.11$, $P < 0.0001$) and by target ($F_{2,549} = 51.03$, $P < 0.0001$) leading to an average increase of 1.19 ± 0.30cm (Target 1: 1.22 ± 0.30cm, $P = 0.0001$, Target 2: 1.11 ± 0.27cm, $P = 0.019$, Target 3: 1.23 ± 0.28cm, $P = 0.0001$) by the

end of the session (Figure 11.d). Movement onset was affected by timepoint ($F_{1,549} = 4.88$, $P = 0.028$) but not target ($F_{2,549} = 1.90$, $P = 0.15$) leading to decrease in onset for Target 1 (31 ± 15ms, $P = 0.014$) and Target 2 (40 ± 21ms, $P = 0.039$) but not Target 3 (23 ± 19ms, $P = 0.35$) by the end of the session (Figure 11.a).

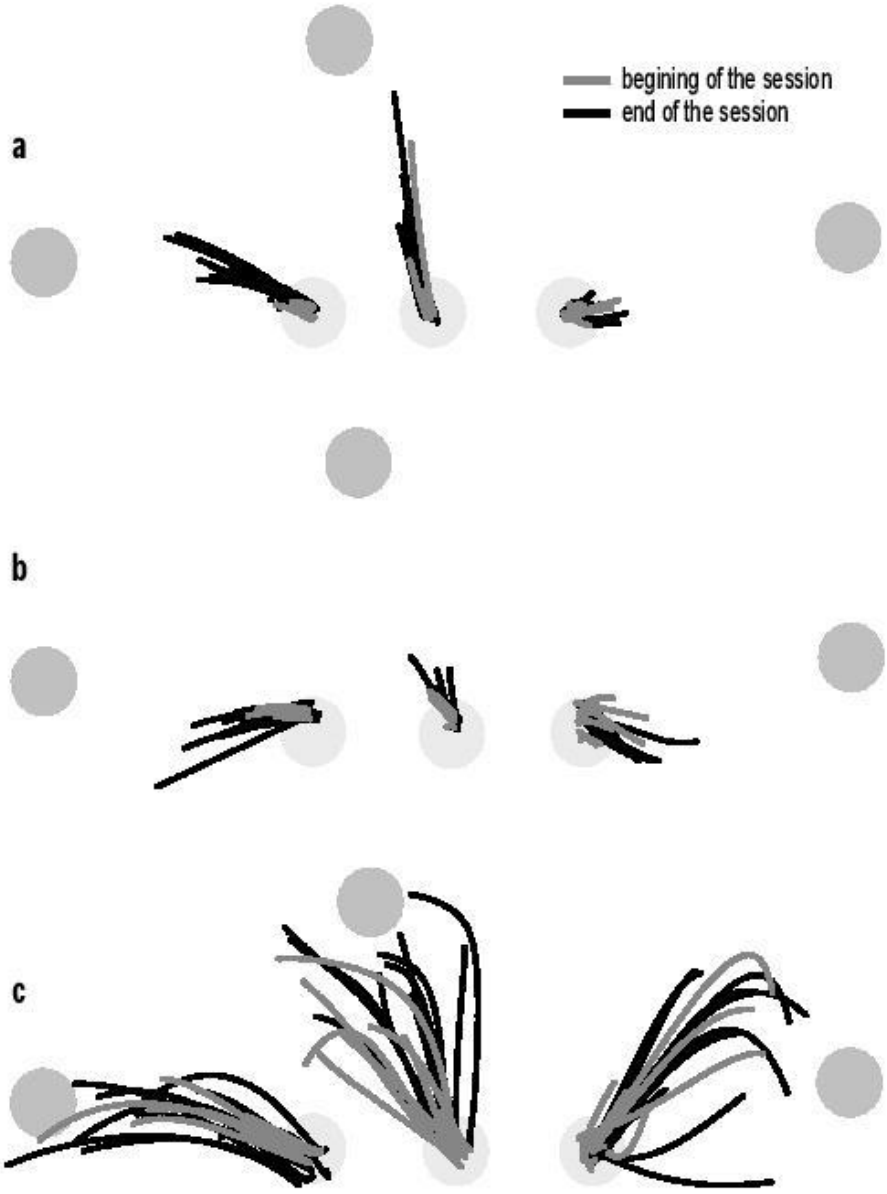

*Figure 10. Beginning and end of the session reach trajectories for 3 representative. The beginning trials in gray and the end trials in black are shown to each target for individuals with (**a**) UEFM = 11, MAS for: elbow flexion = 2, elbow extension = 2, shoulder flexion = 1, shoulder extension = 0, (**b**) UEFM = 19, MAS for: elbow flexion = 3, elbow extension = 3, shoulder flexion = 3, shoulder extension = 3, and (**c**) UEFM = 31, MAS for: elbow flexion = 2, elbow extension = 3, shoulder flexion = 0, shoulder extension = 0. MAS: Modified Ashworth Scale, UEFM: Upper Extremity Fugl-Meyer.*

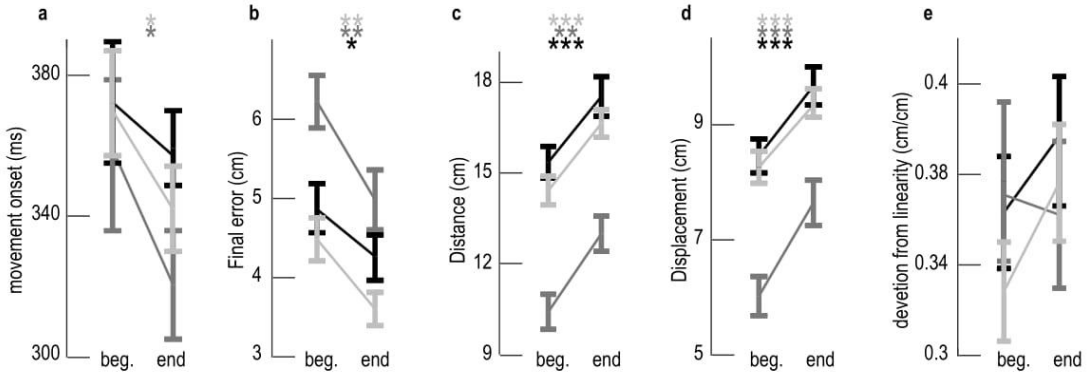

*Figure 11. Group results of movement metrics. Movement onset (a), Final error (b), Distance (c), Displacement (d) and deviation from linearity (e) for the beginning (left) and the end (right) of the session to Target 1 (light gray), Target 2 (dark gray) and Target 3 (black). * P < 0.05, ** P < 0.01, *** P < 0.001 and the error bars are Standard Errors. beg.: 10 voluntary trials at the beginning of the session, end: 10 voluntary trials at the end of the session*

Group results showed that muscle activity onset was affected by timepoint ($F_{1,3573} = 86.88$, $P < 0.0001$), target ($F_{2,3573} = 13.61$, $P < 0.0001$) and muscle ($F_{5,3573} = 5.67$, $P < 0.0001$) (Figure 12). Muscle onset was faster for all muscles at Target 1 (avg $\Delta = 92 \pm 31$ms, all: $P < 0.013$), none of the muscles at Target 2 (all: $P > 0.09$), and all muscles except TRI for Target 3 (avg $\Delta = 69 \pm 27$ms, all: $P < 0.02$; TRI: $P = 0.27$) (Figure 12).

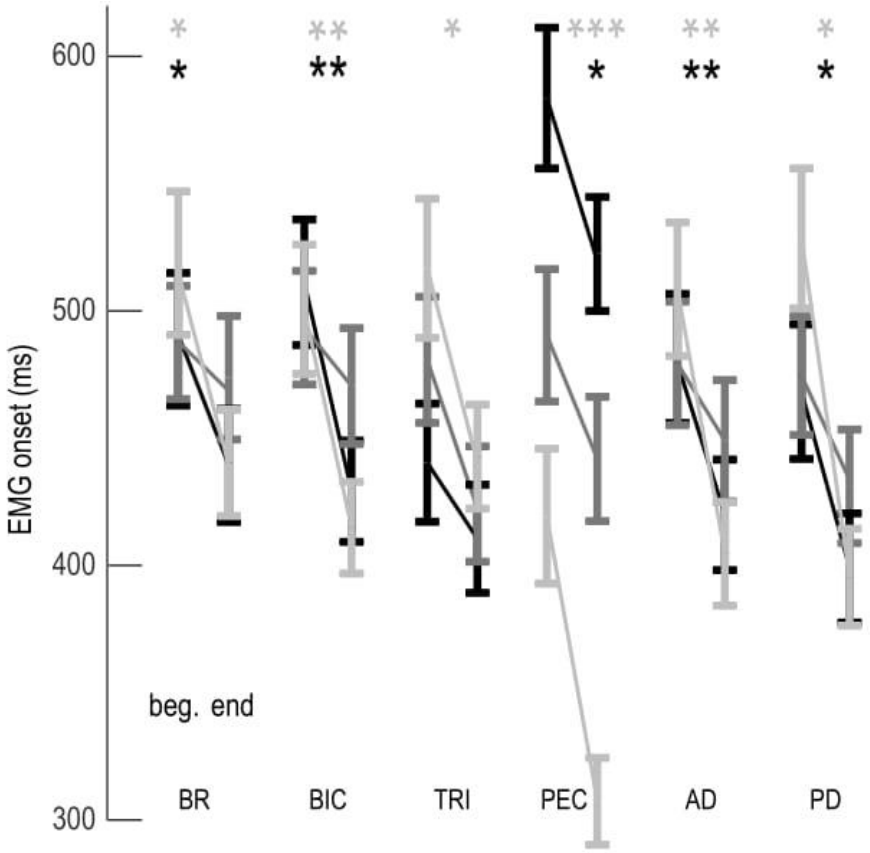

*Figure 12. Group result of muscle activity onset during voluntary trials. EMG onset for the beginning (left) and the end (right) of the session to Target 1 (light gray), Target 2 (dark gray) and Target 3 (black) for each muscle. BR: brachioradialis, BIC: biceps, TRI: triceps lateral head, PEC: pectoralis, AD: anterior deltoid, PD: posterior deltoid. * P < 0.05, ** P < 0.01, *** P < 0.001 and the error bars are Standard Errors. beg.: 10 voluntary trials at the beginning of the session, end: 10 voluntary trials at the end of the session.*

Muscle activity amplitude was affected by timepoint ($F_{1,3573} = 3.75$, $P = 0.05$), target ($F_{2,3573} = 12.34$, $P<0.0001$) and muscle ($F_{5,3573} = 200.2$, $P < 0.0001$). For Target 1, the shoulder horizontal adduction target, activity was increased in PEC ($\Delta = 0.026 \pm 0.01$mV, $P = 0.048$) and decreased in AD ($\Delta = 0.02 \pm 0.02$mV, $P = 0.037$) and PD ($\Delta = 0.073 \pm 0.03$mV, $P = 0.045$). For Target 2, the combination elbow extension and shoulder flexion target, BIC activity was decreased ($\Delta = 0.030 \pm 0.01$mV, $P = 0.007$). For Target 3, elbow extension task, TRI activity was increased ($\Delta = 0.038 \pm 0.02$mV, $P = 0.033$) while BIC ($\Delta = 0.023 \pm 0.01$mV, $P = 0.049$), AD ($\Delta = 0.083 \pm 0.03$mV, $P = 0.0004$) and PD ($\Delta = 0.13 \pm 0.06$mV, $P = 0.042$) were decreased (Figure 13).

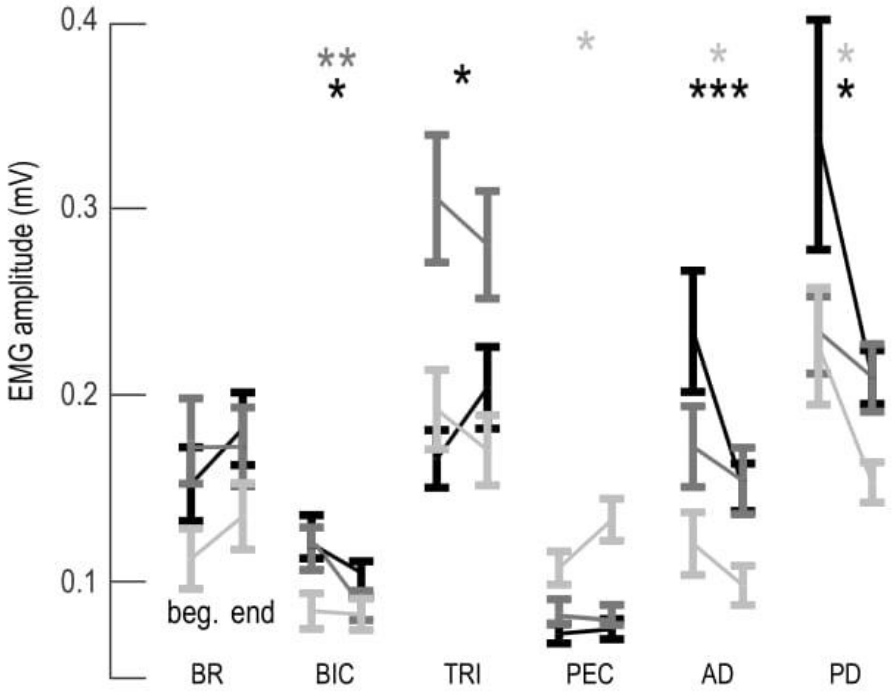

*Figure 13. Group results of EMG amplitude during voluntary movements. EMG amplitude for the beginning (left) and the end (right) of the session to Target 1 (light gray), Target 2 (dark gray) and Target 3 (black) for each muscle. BR: brachioradialis, BIC: biceps, TRI: triceps lateral head, PEC: pectoralis, AD: anterior deltoid, PD: posterior deltoid * P < 0.05, ** P < 0.01, *** P < 0.001 and the error bars are Standard Errors. beg.: 10 voluntary trials at the beginning of the session, end: 10 voluntary trials at the end of the session.*

The presence of abnormal flexion synergies in individuals with moderate and severe stroke has been well document (e.g. proceeding flexor muscle activation during an extensor task) [31], [32], [35], [70], [71], [75]. In addition, heightened EMG amplitude and faster EMG onset of flexor muscles (BR, BIC and AD) was reported during SR reach movements [25]. Therefore, we predicted larger EMG amplitude in flexor muscles during the voluntary trials as the impact of the SR trials. However, our results showed that this prediction was not true.

For Target 1, a shoulder horizontal adduction task, we showed EMG amplitude increases in the PEC muscle, paired with decreases in PD extensor activity in voluntary trials. This is beneficial, as more shoulder horizontal adduction can occur with decreased antagonist extension activity from PD. For Target 2, an elbow extension and shoulder flexion task, we showed a similar decrease in BIC activity during voluntary trials (Figure 13). The decrease in BIC is further evidence that abnormal flexor activity did not

affect Targets 2 and 3, with biceps being a common culprit for post-stroke spasticity [18], [76]. Lastly, for Target 3, an elbow extension task, appropriate increases in triceps activity coincide with decreases in BIC, AD, and PD activity during voluntary trials. Moreover, there was an unexpected increase for TRI (an extensor) for Target 3, allowing for improved reaching distances (Figure 13). In short, flexor EMG amplitudes seem to decrease in the majority of cases for voluntary movements after a SAS session, while extensors (TRI) increase.

3.5 Discussion

It has been demonstrated that SR can improve movement parameters in iwS [17], [20], [24], [25], [29], [65]; however, SR also induces task-inappropriate flexor activity [17], [25], [28] raising concerns that exposure to SR might increase inappropriate activity during voluntarily-initiated movements. For example, the severe group from this dataset had early flexor activation preceding triceps (TRI) while initiating an extension task, limiting reaching distances during SR trials [25]. Thus, the objective of this study was to evaluate the impact of exposure to SR on voluntary-initiated movements (non-startle-evoked) during point-to-point reaching in individuals with moderate and severe stroke. We found that while abnormal flexor activity was present in SR trials during point-to-point reaching in all 3 directions [25], [28], voluntary movements did not see an increase in abnormal flexor activity. In opposition to our hypothesis, agonist muscle activity was increased and task-inappropriate, antagonist flexor activity decreased. Moreover, exposure to SR led to a small increase in subjects' ability to reach farther, start reaching faster, and more accurately. While this represents a short exposure period (~1hour), it suggests that at least short-term exposure to SR does not lead to facilitation of inappropriate flexor synergies, but rather may reduce them, allowing for larger reaching movement.

This study offers the first evidence that exposure to SR in severe-to-moderate iwS 1) is safe and does not lead to increase in task-inappropriate flexor activity during voluntary movement and 2) may improve voluntary reaching movements and reduce abnormal flexor activity. Still, significant further study is required before this can be verified. More robust evaluation of muscle activity via an analytical synergy analysis method (e.g. nonnegative matrix factorization) [77], [78] and under conditions where abnormal flexor activity is highest (arm supported against gravity) [79]–[81] is warranted.

3.5.1 SR for Use in Rehabilitation

The results from this study indicate that exposure to SR decreases abnormal, task-inappropriate flexor activity and increases reaching distance in individuals with severe/moderate stroke, opening the possibility of SR in rehabilitation. Contrary to our hypothesis, the movement distance, onset, displacement, and final accuracy improved for most or all targets as a result of this task. Therefore, exposure to SR did not lead to abnormal flexor activity in voluntary movement, but instead caused decreases in flexor (BIC, AD, PD) EMG amplitudes, and increases in extensors (TRI). This led to an average change of 1.93 ± 0.63 cm in reaching distance, which constitutes an 18% change— larger than what similar studies have reported after longer and more frequent rehabilitation sessions for chronic, severe stroke [70], [82]–[85].

Previous studies evaluating individuals with chronic stroke show small improvements after numerous sessions, highlighting the challenge in making functional changes in individuals with severe/moderate stroke [70], [82]–[85]. Recent studies with a minimum of 10 sessions and therapies ranging from seated training to virtual reality report at most an 11% increase in reaching distances and a 4% increase of range of motion-- even when these novel therapies were paired with conventional physical therapy [70], [82]–[85]. In this study, we see changes in Target 1 (2.38 ± 0.5 cm, shoulder horizontal adduction task) that meet minimal detectable change (>2.3 cm) as measured by the Functional Reach Test [86], provocatively suggesting that SR exposure might induce functionally significant changes. Future controlled studies should evaluate if SR exposure during traditional therapy might enhance reaching in individuals with severe/moderate stroke.

If SR is shown to generate functionally significant changes, understanding the mechanisms will become more important. It is possible that exposure to SR may result in reliance on the brainstem or, given the short-term facilitation, activation of these muscles releases spasticity. The early flexor activation we report [25] during SR trials may result from an interfering hypermetric classic startle response [17], [18], [25]. Not only do iwS have increased ipsilateral projections of the reticulospinal tract [87], [88], but the cortex, which likely mediates the amplitude of a classic startle reflex [28], [69], is damaged post-stroke and can no longer fully suppress a classic startle reflex. This likely causes task-inappropriate flexion when

iwS' movements are paired with a startle, while in healthy individuals, SR only elicits the planned movement [20], [38], [60]. During voluntary trials that are not preceded by a SAS, the subject can initiate their movement uninterrupted by classic startle, while also becoming more practiced in the task. An alternative mechanism may be that SR over-activates flexor muscles, leading to decreases in neglect-related spasticity. When SR is used to elicit movement in iwS, flexor activity surpasses the maximum voluntary contraction (MVC) in individuals with severe stroke by 2 to 3 times [25]. This over-activation of paralyzed muscles may mimic the effects of functional electrical stimulation (FES), which decreases spasticity and increases range motion [89]. While the mechanisms driving this success are not fully understood, electrical activation of muscle may free paralyzed cross-bridge attachments and allow infiltration of ions associated with muscle contraction, "releasing" the spastic muscles [89]. It is reasonable to expect that SR generates a similar outcome, given the over-activation achieved. In conclusion, future studies should evaluate both neuroplastic modulation of the brainstem as well as spasticity release as potential mechanisms driving SR-related changes in movement-- both SR and voluntary.

3.5.2 Limitations and Future Directions

Though this study demonstrates that short-term exposure to SR does not lead to facilitation of inappropriate flexor synergies, whether or not it decreases abnormal patterns of activity (leading to enhanced extension) is still unclear. The reaching distance improvements seen here could simply be the result of practice over the session. Future controlled studies should include a control group to evaluate this effect. Additionally, the voluntary trials analyzed at the beginning and end of the session were selected from blocks that included 5 SAS trials. Future studies should ideally include have voluntary trials that have not been contaminated by SAS trials, but instead be performed as blocks without any startling stimuli.

Above we report that Target 1 showed a functionally relevant change in reaching distances, but that this effect did not carry over to the other targets. Targets 2 and 3 did not achieve this functional threshold. This could result from small sample size and a mere 11 cm target distance; however, we also see improvements in accuracy, with final error showing an average decrease of 0.83 ± 0.31cm (all targets $p < 0.013$). Additionally, the minimal detectable change was defined using a different setup with a larger

workspace [86], which allowed for more freedom of movement. Here, participants were limited by a table to constrain movements to two dimensions. Future studies evaluating this question should address the size of the workspace so that movements are not as limited, but the fact that we see such large changes despite these limits is promising.

3.6 Conclusion

In conclusion, exposure to SR does not impair voluntary reaching, but rather decreases abnormal flexor activity and increases reaching performance. This result indicates that at least short-term exposure to SR is safe and opens up the possibility of SR being used for rehabilitation.

CHAPTER 4

4 INVESTIGATING THE CAPACITY OF SR EXPOSURE TO ALTER QUANTITATIVE MUSCLE SYNERGIES OF VOLUNTARILY-INITIATED MOVEMENTS IN IWS.

4.1 Abstract

Background: The abnormal flexor muscle activations are elevated during StartReact (SR) trials in individuals with stroke, especially those with higher impairment and spasticity. There is concern if this increased abnormality would aggravate the muscle synergies of voluntary initiated movements. The previous studies showed enhancement in the voluntary movement and onset/amplitude of muscle activations, but no study has assessed the muscle synergy changes after exposure to the SR.

Objective: The objective of this study is to evaluate the muscle synergies during a session of SR point-to-point reaching task. We hypothesized that the muscle synergy of the individuals with moderate and severe stroke will shift towards the normal after exposure to SR. We expect increase in similarity indices of muscle synergy of individuals with severe and moderate stroke.

Methods: Data was collected from the impaired arm of 20 individuals with stroke and both arms of 9 unimpaired control subjects performing 135 trials of point-to-point reaching to 3 targets. 1/3rd of the trials had startling acoustic sound (SAS) replaced by the go cue. Non-negative matrix factorization method was used for extracting the muscle synergies from EMG data out of 6 muscles, with minimum 90% global Variance Accounted For (gVAF).

Results: Individuals with severe stroke had abnormal brachioradialis and triceps activities in shoulder horizontal adductor and elbow flexor synergies respectively, at the beginning of the session. Both of these abnormalities disappeared at the end of the SR session, resulting in no difference in similarity indices between the severe group and the norm synergy.

Conclusion: This result indicates that SR improves the elbow muscle synergies and short-term exposure to SR is safe and triggers the interest for more investigations of using SR in rehabilitation.

4.2 Introduction

Muscle synergies in neurological intact individuals are robustly invariant and consist of limited sets of muscle activation patterns [77], [90]. However, iwS have muscle synergy abnormalities, correlated with their impaired movements [80], [91]–[95]. These abnormalities are observed more in individuals with severe impairment and as merging of muscle synergies (abnormal co-contraction of muscles) [72], [92], [96], [97].

Abnormal flexor synergy is one of the abnormal synergies in iwS and is known as the main reason for impaired reaching movement [33]. Recent SR studies in stroke have shown that startle triggers more abnormal flexor activities during SR trials [18], [25] and these inappropriate flexor activities increase with the level of impairment [25], [65]. The EMG amplitude of the flexor muscles reached more than twice maximum voluntary EMG amplitude during the SR trials [25] and it was more noticeable in biceps [18], [25] during SR trials. Therefore, there is concern about voluntary initiated movements after exposure to SR to carry some part of this outcome, leading to aggravating their muscle synergies during their movements. Our recent study, has suggested that exposure to SR might result in decrease of abnormal muscle synergies, by showing that one session of SR point-to-point reach movement enhances the distance, accuracy and onset of the movement, and increases the extensor muscle activities while diminishing some of the flexor muscle activities during the voluntary initiated movements in iwS (chapter 3). However, a muscle synergy analysis has not been completed to confirm this suggestion. Clinical assessments, and behavioral tests before and after training express information about movement alterations, but Muscle synergy analysis (MSA) serves as a deeper analysis for assessing the changes of central nervous system programming the movement [77], [91], [92], [94], [98]–[102]. Therefore, assessing the muscle synergy changes is necessary for evaluating a therapy method [94], [100]. Thus, the objective of this study is to investigate the muscle synergies of point-to-point voluntary-initiated reaching movements of iwS after exposure to SR.

Muscle synergy is defined as invariant coactivation of a group of muscles to perform a subtask. MSA can find these groups of muscles and their ratio for each subtask out of the EMG data collected [77],

[98], [99]. MSA reduces the dimensions of the EMG data using component analysis algorithms and focuses on the most related groups of muscles for each task [77], [98], [100], [103], [104]. In this study, we extract and compare the muscle synergy data from the beginning and end of the reach training of the individuals with mild, moderate and severe stroke and an age-matched control group. We hypothesize that the number of muscle synergies in individuals with severe and moderate stroke will increase during the session to reach the same number as individuals with mild stroke and unimpaired control group. We also hypothesize that there are abnormalities in the muscle synergies of individuals with moderate and severe impairment at the begging of the session, however, these abnormalities disappear at the end of the session, meaning the the similarity indices will increase at the end of the session. We expect the abnormal synergies appear as the coactivation of the flexor muscles.

4.3 Methods

4.3.1 Subjects

Data was collected from the impaired arm of 20 individuals with chronic stroke (age = 52.4 ± 16.6 years) (Table 1) and both arms 9 unimpaired control subjects (age = 51.5 ± 21.2 years, including 5 female and 4 male subjects). The individuals with stroke were divided to three sub-groups according to their Upper Extremity Fugl-Meyer (UEFM) score: 5 severe (UEFM <25), 6 moderate (25 < UEFM < 45) and 9 mild (45 < UEFM). Inclusion/exclusion criteria included no injury to arm/shoulder in past 6 months, at least 6 months post-stroke, no hearing loss/sensitivity, no dizzy or fainting spells, no seizure or heart attacks, measurable impairment in the upper extremity, and could not be pregnant. This study was approved by Arizona State University's Institutional Review Board STUDY00002440. Subjects were informed of potential risks prior to participation in the study and verbal/written consent was obtained.

Table 3. Summary of subjects' characteristics

Number	Sex	Age (years)	Duration from onset of stroke (years)	Paretic arm	UEFM Score	Modified Ashworth Score			
						Shoulder flexion	**Shoulder extension**	**Elbow extension**	**Elbow flexion**
1	M	31	0.9	R	65	0	0	0	0

2	M	77	3.7	R	25	0	0	3	3
3	M	59	5.3	L	41	0	1	0	1+
4	M	36	10.4	*R>L	31	0	0	3	2
5	F	66	4.7	R	66	0	0	0	0
6	M	61	1.7	L	55	1	1	1+	0
7	F	61	1.6	L	64	0	0	0	0
8	M	47	1.5	L	61	0	0	0	0
9	F	39	3.7	R	19	3	3	3	3
10	M	51	1.1	L	24	0	1	3	3
11	M	28	0.5	R	35	0	0	2	2
12	M	52	11.7	L>R	58	0	0	0	2
13	M	71	12.4	L	8	1	1	3	4
14	F	65	17.4	R	65	0	0	0	0
15	F	49	1.2	L	11	1	0	2	2
16	F	65	7.8	L	11	0	1	1+	0
17	F	19	0.8	L>R	14	0	0	0	1
18	M	70	2.5	L	64	0	0	0	0
19	F	33	13.5	R	11	1	1	1	1
20	M	68	3.3	R	53	0	0	0	0

*UEFM: Upper Extremity Fugl-Meyer, **R > L means both arms are impaired, but the right arm is more impaired, therefore, the UEFM and Modified Ashworth Scales are measured for the right arm.

4.3.2 Protocol

We used the same protocol and system as our previous studies [25]. Briefly, Ag/Cl surface electrodes were used to record (Electromyography) EMG activity data from the brachioradialis (BR), biceps (BIC), triceps lateral head (TRI), pectoralis (PEC), anterior deltoid (AD), and posterior deltoid (PD), left (LSCM) and right (RSCM) sternocleidomastoid muscles. We refer readers to our previous papers (Rahimi and Honeycutt 2020, chapter 3) for more specific details about the EMG and movement recording systems and the initial processing on the raw data.

Subjects sat in the experimental chair with their arm being supported on an arm support with minimum friction and with an initial arm position of shoulder abduction at 70°, shoulder flexion at 40°, and elbow angle at 90° (all ±5° to subjects comfort). The arm support was custom made by adding wheels to

the bottom of a board, in order to minimize the friction with the table and support the arm weight against gravity. Their arms were attached to this arm support using a strap. The instruction given to the subjects was to perform point-to-point reaching movements from a fixed home position to three target circles. Targets were designed to cover most of their horizontal workspace and included mostly shoulder horizontal adduction (Target 1), mostly elbow extension (Target 3), and combination of shoulder flexion and elbow extension (Target 2) (Figure 14). They could see the home and target circles on a monitor in front of them, with a cursor depicting the online location of their hand as visual feedback. The distance between home and target circles was specific to each individual and was a function of their arm lengths: $R = \frac{\sin(70^o) \times length\ of\ upper\ arm + length\ of\ forearm}{5}$.

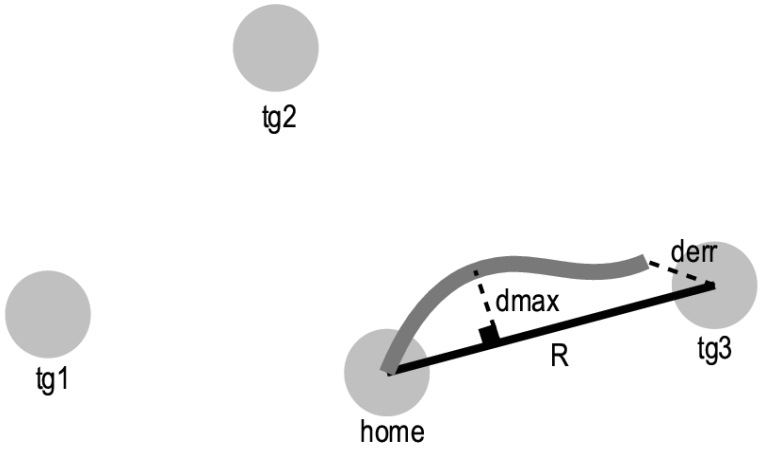

Figure 14. Target Positions. The locations of target and home circles for the right arm are presented. The left arm targets were the mirror image of these targets. R was the distance between the home circle and the target circles (black line). The gray line is the movement trajectory from the start point to the end point. dmax is the maximum distance between the movement trajectory and the axis connecting the home to the target. derr is the distance between the target and the end point. tg: target.

Prior to the main session, subjects practiced reaching 15 times to each target with online visual feedback of the cursor to make sure they learned the instruction. These trials were not included in the analysis. They were asked to move following two soft (80 dB) auditory sounds. The instruction was to get ready after the first sound and reach as fast and accurate as possible after hearing the second sound (GO). GO cues were delivered between 2-3 seconds after the get ready cues to prevent anticipation.

Following practice, the cursor position feedback during the movement was removed, meaning the cursor disappeared as soon as the subjects left the home circle. They were notified of their final position accuracy by reappearing the cursor after they stopped.

Subjects performed 45 reaches to each target (135 total reaches) separated into blocks of 15 reaches to a single target. The order of blocks was randomized. A Startling Acoustic Stimulus (SAS) of 115dB was randomly replaced with the GO cues during 1/3 of trials. For more details about this sound and the system producing it refer our previous paper [25]. Upper Extremity Fugl-Meyer assessments (UEFM) were performed from the iwS subjects at the end of the session to classify them to mild-, moderate-, and severe-stroke groups.

4.3.3 Data Analysis

4.3.3.1 EMG processing

First and last 10 voluntary reaches to each target were labeled as the beg. (beginning) and the end. We did not include SAS trials at this part. EMG of the 6 muscles (BR, BIC, TRI, PEC, AD and PD) was cut between the 2 consecutive 10% of the peak velocity value [94]. The baseline data was 500ms before any movement. EMG processing included removing the DC component, rectifying and removing the baseline. The baseline was removed by subtracting the mean of the baseline from the EMG data, which resulted in occasional negative values in the data. Therefore, all the negative values were set to zero to make sure there is no negative value during MSA matrix decomposition. Next, low pass filtering (4^{th} butter worth) and resampling (cut off frequency = 10Hz and sampling frequency = 3000Hz) were applied on the data. We normalized the data using the maximum EMG among the trials. Finally, the EMG for each muscle was concatenated across trials and targets for the identification of muscle synergies.

4.3.4 Muscle Synergy Analysis

4.3.4.1 Identifying muscle synergies

The computational method used for extracting muscle synergies was non-negative matrix factorization (NNMF) which creates a parts-based representation of the final signal using only positive, additive components (Lee and Seung, 1999). This method would model the EMG as linear combinations of a set of N muscle synergies: $\mathrm{EMG} = W_{m\times N}.C_{N\times t} = \mathrm{w1.c1} + \mathrm{w2.c2} + \cdots$. Following optimization

problem was defined and solved for finding the W for each subject at the beginning and end of the session:

$$\min_{s.t.\ W,C>0} \left|\left|EMG - W.C\right|\right|$$

where EMG is the EMG data as a m × t matrix (m : number of muscles (6 in this case), t: number of total data points) and W is the m × N synergy matrix and C is the N × t coefficient matrix. N is the number of synergies.

Each synergy in matrix W was normalized using the magnitude of the synergy vector and the activation coefficients of each synergy were scaled by the magnitude of the corresponding synergy vector.

After extracting the synergies, they were matched using a synergy template for comparison purposes. The synergy template was chosen manually from each group and the similarity between other synergies and the template synergies was calculated. Then we ordered the synergies for each subject according to the most similarity to the synergy template. Finally, the matched synergies were checked manually to prevent any misplacements [97].

4.3.4.2 Number of muscle synergies

We calculated the variance accounted for (%VAF) based on the entire dataset as a function of the number of synergies varying from 1 to 6. $\%VAF = 100 \times (1 - \frac{SSE}{SST})$, where SSE is sum of the squared residuals and SST is the sum of the squared EMG data [97], [105]. We calculated the VAF for the whole EMG data (global VAF or gVAF) and for each muscle (muscle VAF or mVAF). We calculated the minimum number of synergies to suffice the minimum gVAF of 90% and minimum mVAF of 60%. We added a local criterion to have maximum 3% increment in gVAF by adding one more synergy. The mean number of synergies for each group was around number 4 (3.5 < mean of number of synergies < 4.5). Specifically, a set of 4 synergies is required to obtain gVAF > 90%, mVAF > 60% and ΔgVAF < 3% for each subject. Thus, we extracted 4 synergies for each subject.

4.3.4.3 Similarity of synergies

To quantify the similarity between synergies in different groups at the beginning and the end of the session, respectively, we used the following methods: 1) visual comparison: by plotting the bar graph

of the mean synergy in each group to have a visual sense of muscle synergy changes during the session for each group. 2) Percentage of similarity to the control dataset: Scalar product (r-values) for each subject was calculated as the scalar product of each subject's synergy with the norm synergy (mean synergies of the control group). The control dataset was the data collected from the both arms of the unimpaired, age-matched group. The similarity indices were calculated for the right and left arms of the unimpaired individuals to make sure that the synergies of the right and left arms were similar in the control group [91], [97]. The data sets with r-values more than 80% was defined as being similar to the norm synergy and the percentage of the similarity to the control group was defined as the percentage of datasets in each group with a synergy similar to the norm synergy. The r-valure in each group were compared to the control group using the Gardner-Altman two-groups t-test (95% CI).

We hypothesized that H1) the number of muscle synergies in individuals with severe and moderate stroke will increase during the session to reach the same number of synergies as in individuals with mild stroke and control subjects. We also expect to see abnormalities in the composition of muscle synergies of individuals with moderate and severe impairment at the begging of the session. This implies that H2) the scalar products and percentage of similarity to control datasets for severe and moderate groups are lower at the beginning. However, we expect that these abnormalities disappear at the end of the session, i.e., H3) there will be no difference in scalar products and % similarities with the norm synergy at the end of the session.

4.4 Results

4.4.1 Number of Synergies

The number of synergies that would meet the criteria to estimate the appropriate number of synergies for this study (i.e., gVAF > 90%, mVAF > 60% and gVAF difference < 3%) was 4 synergies. Finding the number of the synergies is an important step in MSA. The group average of the number of synergies was around four (between 3.5 to 4.5) for acceptable ranges of mVAF (40 to 80%), gVAF (80 to 92%) and gVAF difference (3, 4 and 5%). More specifically, number 4 is the closest natural number to the average of the number of synergies needed each group to address gVAF > 90%, mVAF> 60% and gVAF

difference < 3%. The percentages of datasets with minimum number of synergies to provide requirements mentioned above (i.e. gVAF > 90%, mVAF > 60% and gVAF difference < 3%.) are shown in Figure 15. Moderate and severe group had more data requiring 4 synergies at the beginning of the session but it reduced at the end and shifted to a few more subjects requiring 5 minimum synergies. The opposite of this happened for mild group. Overall, the stroke groups required fewer number of synergies on average, 75% of the stroke data sets required ≤ 4 synergies compared to 57% of the unimpaired group (for both the beginning and the end of the session conditions).

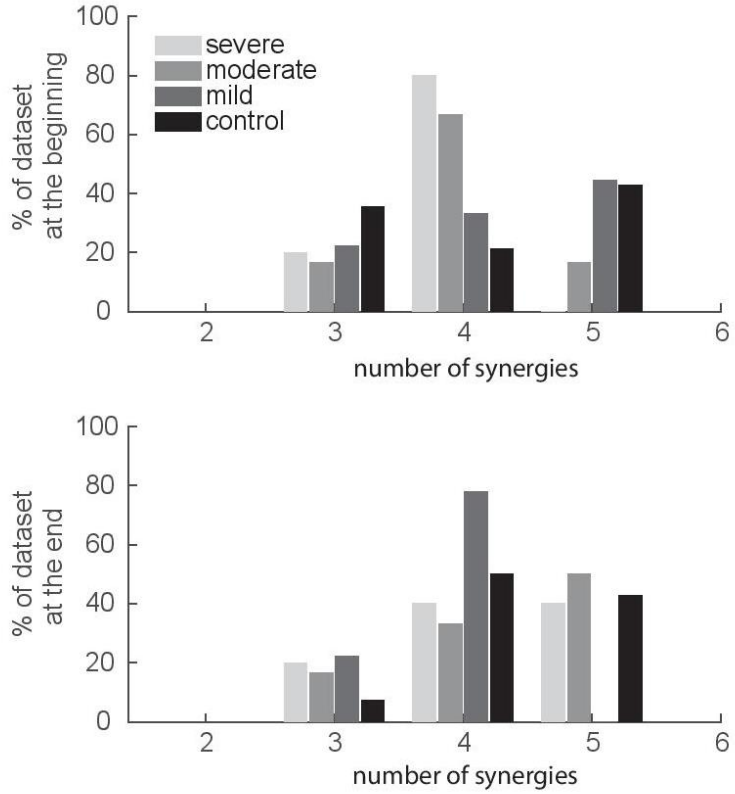

Figure 15. Percentage of datasets requiring 3, 4 and 5 minimum synergies. The number of subjects in each group who would require minimum 3, 4 and 5 synergies to fulfill gVAF > 90%, mVAF >60% and gVAF difference < 3% are devided by the total number of subjects in each group and presented as percentages at the beginning of the session (top) and the end of the session (bottom).

The exact number of synergies identified for each group at the beginning were 4.1 ± 0.37 for the control group, 4.2 ± 0.26 for the mild stroke group, 3.8 ± 0.18 for the moderate stroke group and 4.0 ±

0.24 for the severe stroke group. These numbers were 4.3 ± 0.28 the control group, 3.78 ± 0.14 for the mild stroke group, 4.5 ± 0.2 for the moderate stroke group and 4.0 ± 0.33 for the severe stroke group at the end of the session. The number of synergies across groups and conditions were not significantly different ($P > 0.45$ for all of them). In cases with more than four synergies required, the gVAF was still larger than threshold defined and the one more synergy was to fulfill the mVAF. The gVAFs for 4 synergies were on average 96.6 ± 0.2 % for beg. and 96.4 ± 0.2 % for end for control subjects, and 97.2 ± 0.4% for beg. and 96.8 ± 0.6 % for end for the stroke subjects (mild, moderate and severe). Overall, 4 was a solid number for the number of synergies, so we extracted 4 synergies for each subject to simplify the comparisons.

4.4.2 Synergies

Each synergy contains specific characteristics of movement. Figure 16 is the norm synergy, calculated as the mean of the control group dataset at the end of the session.

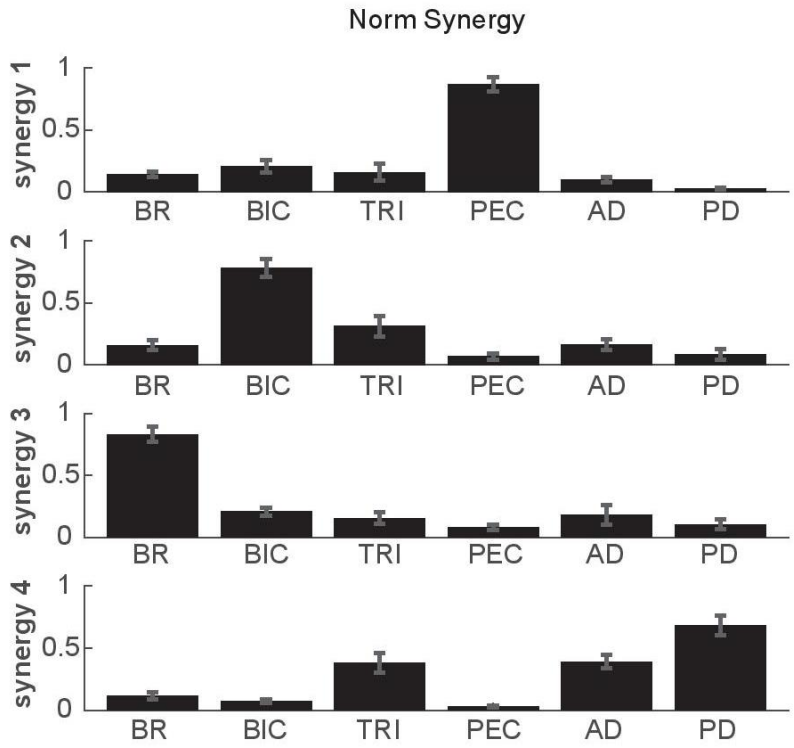

Figure 16. The norm synergies. The group average of the voluntary-initiated movement synergy in control group (right and left arm of the unimpaired individuals at the end of the session).

Synergy 1 is a shoulder horizontal adduction synergy (target 1), so it is mainly PEC muscle activation (Figure 17). Individuals with severe stroke have different shoulder horizontal adduction synergy ($P = 0.03$) to the norm synergy at the beginning of the session (similarity = 20%). The main difference is produced by coactivation of BR and PEC at the beginning (Figure 17). The BR abnormal activation did not appear in moderate and mild groups, so they remained similar to the norm synergy.

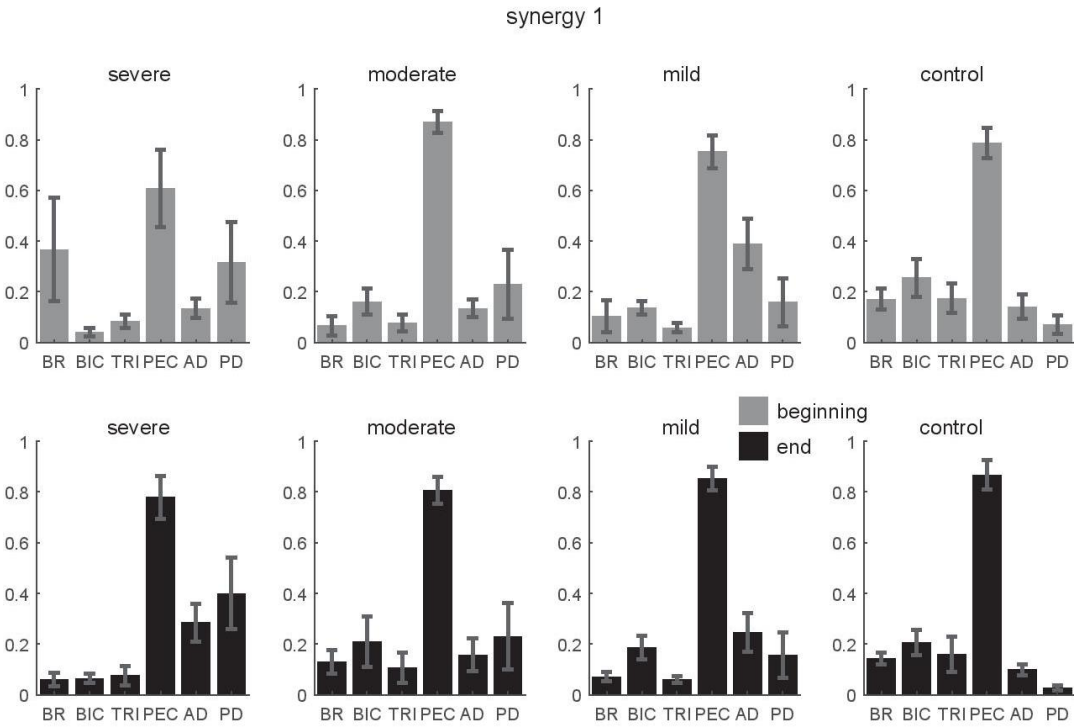

Figure 17. Synergy 1. Shoulder horizontal adduction synergy of voluntary-initiated movements of each group at the beginning (gray bars) and end (black bars) of the session.

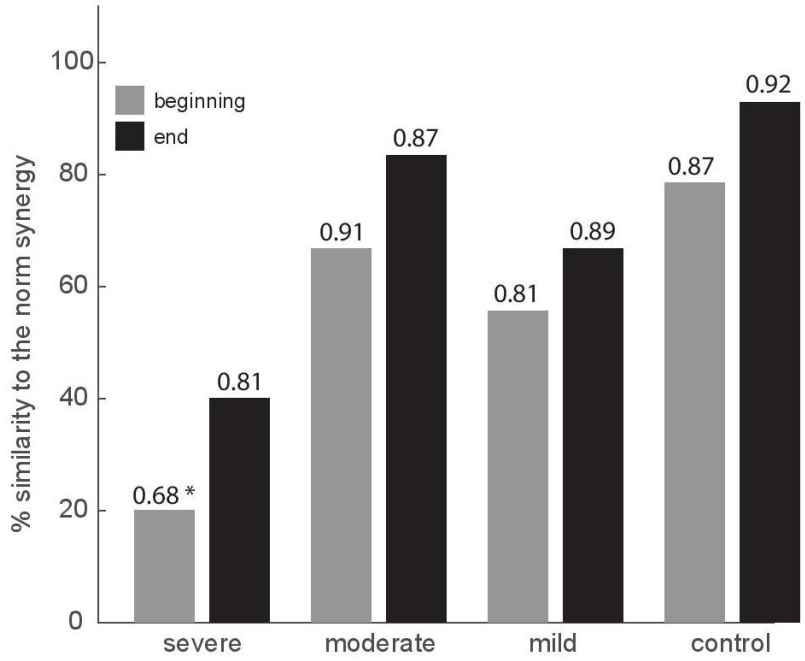

*Figure 18. Percentage of similarity between each group and the norm synergy are represented as bars. The mean of scalar products between synergy 1 of each group and the norm synergy are represented as the number above the bars. The statistical significance of scalar product difference between each group and the control dataset (the dataset of the control group at the end of the session) are represented next to each number as following: * P < 0.05, + 0.05 < P < 0.1.*

Synergy 2 is an elbow flexor and extensor activation synergy, consisting of BIC, TRI and BR as the most contributing muscles (Target 1,2 and 3) (Figure 19). This synergy is the same for both conditions in all the groups (similarity > 55%, min scalar product average > 0.79 with P > 0.2 for all) except for the mild end dataset (similarity = 44%, scalar product average = 0.47 with P = 0.02) since they had larger activation of AD at the end of the session.

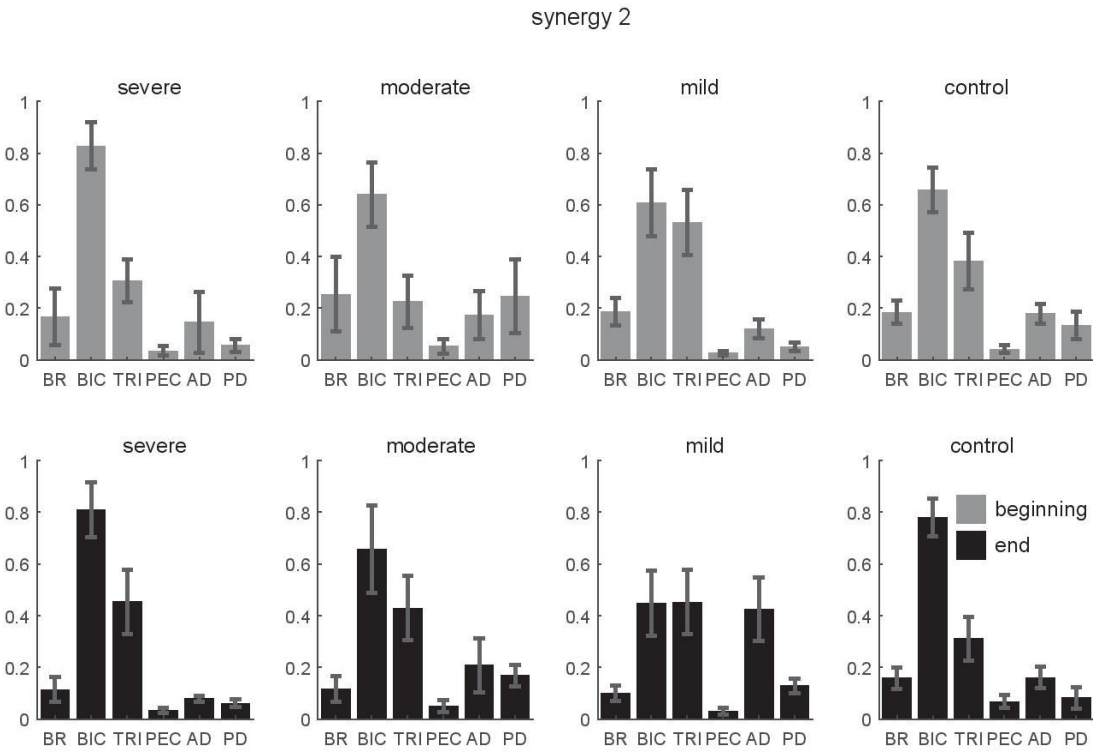

Figure 19. Synergy 2. Elbow movement synergy of voluntary-initiated movements of each group at the beginning (gray bars) and end (black bars) of the session.

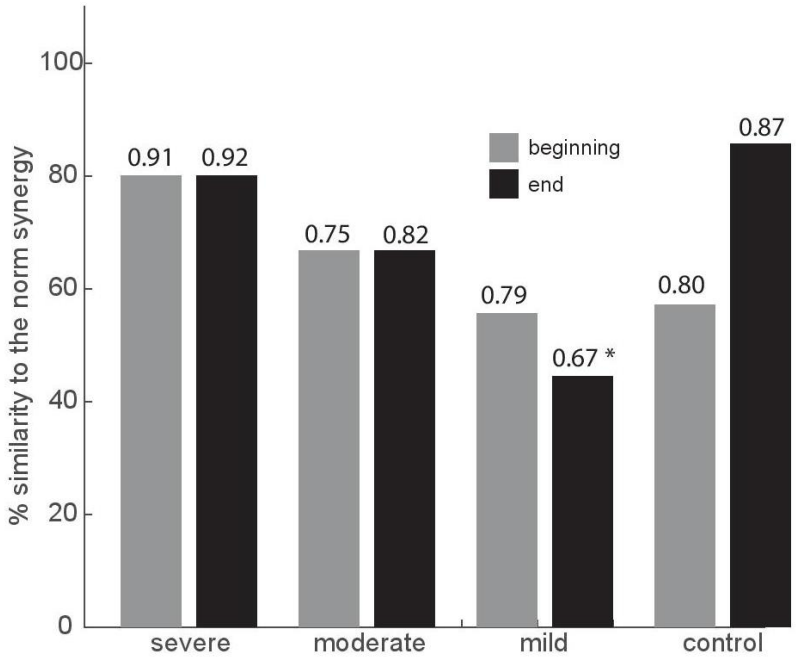

*Figure 20. Percentage of similarity between each group and the norm synergy are represented as bars. The mean of scalar products between synergy 2 of each group and the norm synergy are represented as the number above the bars. The statistical significance of scalar product difference between each group and the control dataset (the dataset of the control group at the end of the session) are represented next to each number as following: * P < 0.05, + 0.05 < P < 0.1.*

Synergy 3 is an elbow flexor synergy and the main muscle activated at this synergy is BR (Target 1) (figure 21). Severe group had an abnormal coupling of TRI and BR at the beginning of the session. Therefore, this group had lower similarities at the beginning of the session (similarity = 40%, scalar product average = 0.59 with P = 0.02). This abnormal coupling disappeared at the end of the session, resulting in similar synergy to the norm for the severe group (similarity = 100%, scalar product average = 0.95 with P = 0.5). The rest of the groups were similar to the norm flexor synergy during the session (similarity > 56 %, scalar product average > 0.76 with P > 0.09).

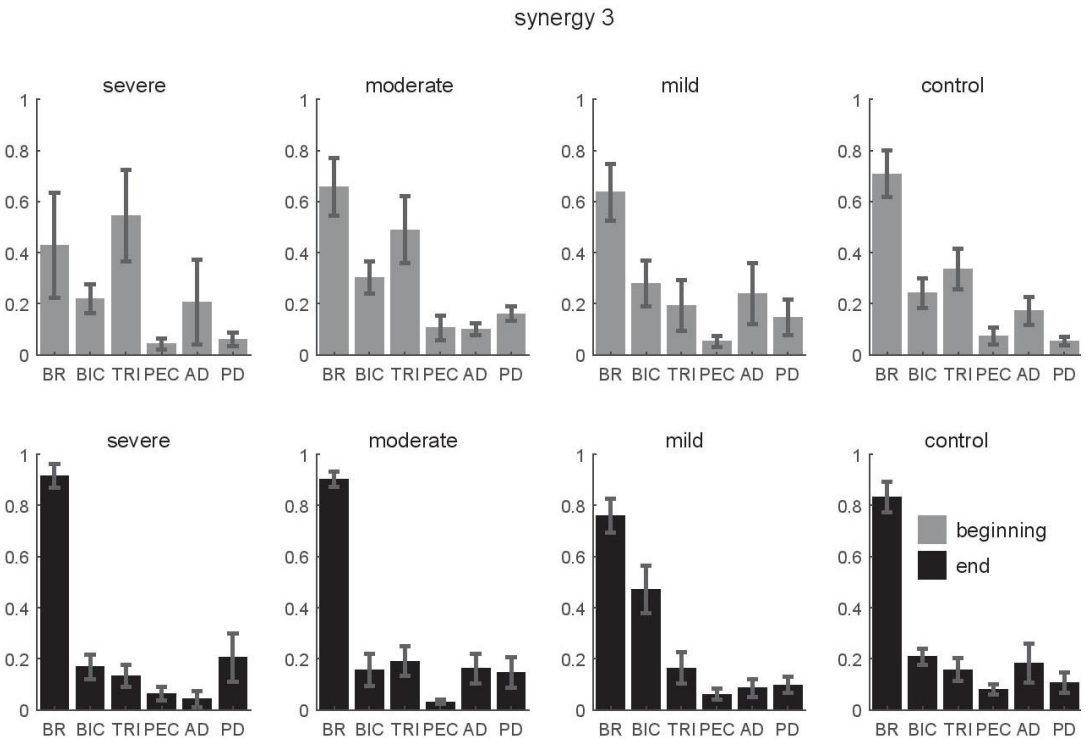

Figure 21. Synergy 3. Elbow flexion synergy of voluntary-initiated movements of each group at the beginning (gray bars) and end (black bars) of the session.

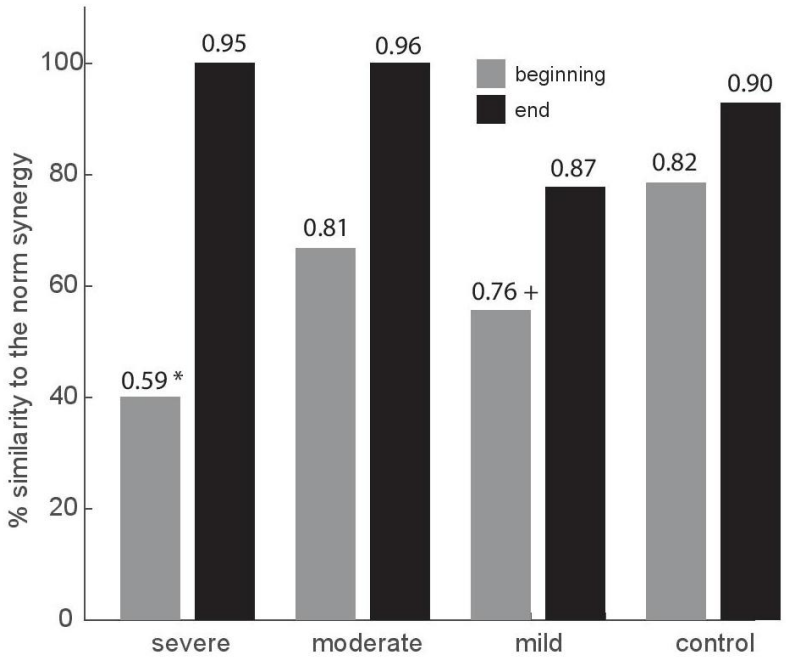

*Figure 22. Percentage of similarity between each group and the norm synergy are represented as bars. The mean of scalar products between synergy 3 of each group and the norm synergy are represented as the number above the bars. The statistical significance of scalar product difference between each group and the control dataset (the dataset of the control group at the end of the session) are represented next to each number as following: * P < 0.05, + 0.05 < P < 0.1.*

Finally, synergy 4 is a shoulder abduction and elbow extension synergy (target 2 and 3) (Figure 23). The severe group had a different behavior for this synergy. They had similar synergy to the norm at the beginning session (similarity = 40 %, scalar product average = 0.80 with P = 0.08) but it became different by the end of the session (similarity = 20 %, scalar product average = 71 with P > 0.009). The moderate group was different from the norm synergy during the session (similarity = 50 %, scalar product average > 0.76 with P < 0.04). The mild group was similar to the norm synergy during the session (similarity > 67 %, scalar product average > 0.81 with P > 0.08).

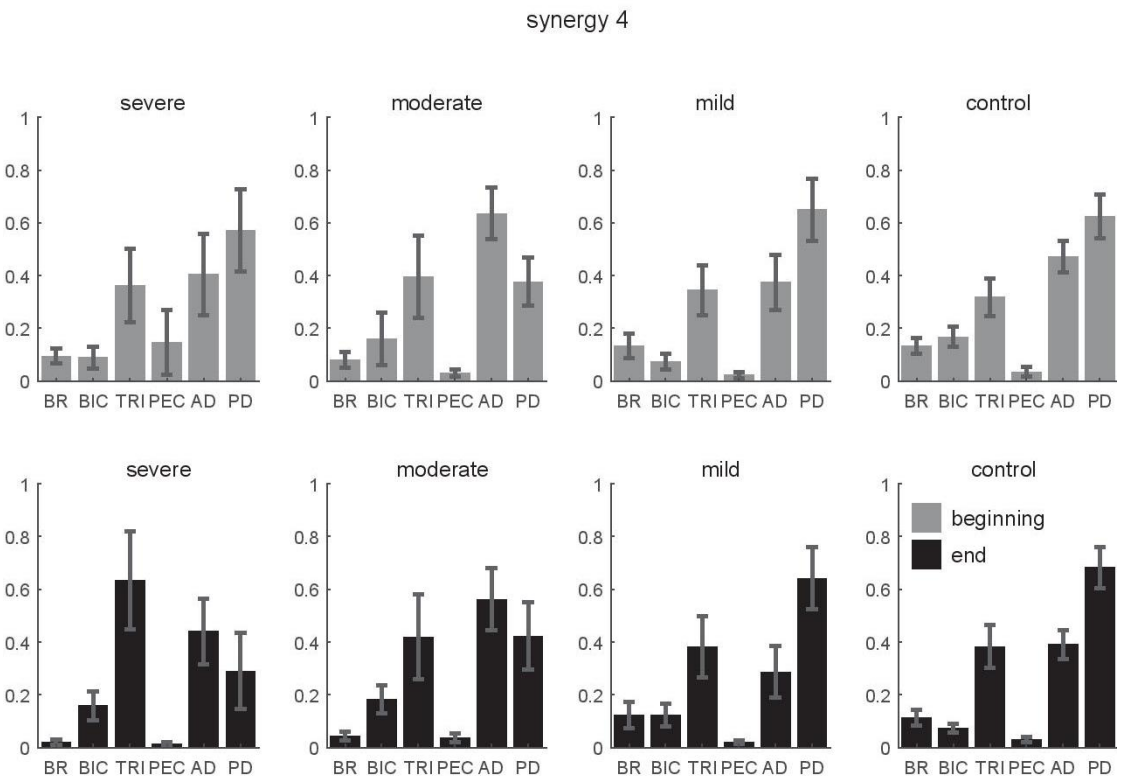

Figure 23. Synergy 4. Elbow extension and shoulder abduction synergy of voluntary-initiated movements of each group at the beginning (gray bars) and end (black bars) of the session.

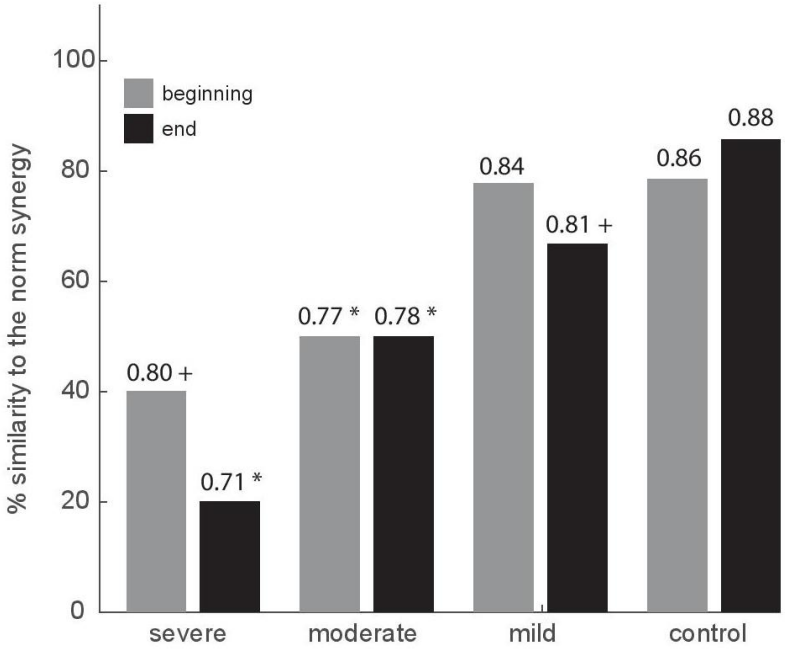

*Figure 24. Percentage of similarity between each group and the norm synergy are represented as bars. The mean of scalar products between synergy 4 of each group and the norm synergy are represented as the number above the bars. The statistical significance of scalar product difference between each group and the control dataset (the dataset of the control group at the end of the session) are represented next to each number as following: * $P < 0.05$, + $0.05 < P < 0.1$.*

4.5 Discussion

4.5.1 Summary

The objective of this study was to quantify the muscle synergies of the iwS with deferent levels of impairments at the beginning and end of the startle point-to-point reach session. The hypothesis was upheld for the number of muscle synergies in severe and moderate group and for the shoulder horizontal adduction and elbow flexion muscle synergies of the individuals with severe stroke but not for the moderate group. The opposite of the hypothesis was true for the shoulder abduction/elbow extension synergy for the severe group.

4.5.2 Number of Muscle Synergies

The number of the muscle synergies was not significantly lower for stroke group but more individuals in moderate and severe group required fewer numbers of synergies for the same accuracy requirement at the beginning. Recent studies showed that individuals with moderate and severe stroke

have alteration in their muscle synergy [97] and this alteration usually involves merging the synergies [92], [106]. Therefore, individuals with moderate and severe synergy usually have fewer number of synergies [92], [95]. However, this study showed that subjects from moderate and severe group –who saw improvement in their voluntary movement (chapter 3)–, required more number of the synergy for the same criteria (i.e. gVAF, mVAF and gVAF difference) at the end of the session (Figure 15). The parentages of the datasets requiring 4 and 5 number of synergies in moderate and severe groups were around the same level of the control datasets at the end of the session (~50%). This suggests that from the number of synergy point of view, individuals with moderate and severe impairment approached those of the control group.

4.5.3 Synergies Extracted

Synergy 1 and 3 changes indicate that the individuals with severe stroke got more similar to the control group by decreasing the abnormal BR activation in synergy 1 and decreasing the abnormal TRI activation in synergy 3. There are evidences that the abnormal muscle synergies in individuals with severe and moderate stroke are correlated with more reliance on lower structures in the brain [31], [35], [70]. This study shows that triggering the lower parts of the brain via SR would not aggravate the abnormal synergies; In contrast, exposure to SR pushes the muscle synergies in these individuals towards the norm synergy.

In addition, in introduction we stated this concern that there are inappropriate flexor muscle activities in iwS, that are heightened during SR trials in iwS, especially subjects with higher spasticity/impairment [18], [25]. This concern is also addressed by the changes in synergy 1, since BR is one of the flexor muscles involving in the abnormal flexor activities in individual with stroke. This result indicates that the startle reaching session helped alleviate some of the abnormal flexor activity as well as other inappropriate muscle activations in these individuals relative to the beginning of the session.

The abnormal AD and PD co-activation during shoulder abduction and internal rotation has been reported in previous studies as compensation strategy to sift the arm gravity support from the arm's muscles to the shoulder muscles [107]. The AD and PD abnormal coactivation appeared in the synergy 1 indicates that although the arm is supported against gravity, the iwS use the deltoids assistance to

perform the shoulder horizontal adduction during the whole session (existed at the beginning and at the end), versus the control group who perform the same task with mainly activating the PEC muscle.

Finally, the reverse changes in synergy 4 for severe group and synergy 2 for mild group are arguable. First, the range of the changes in synergy 4 is not as large as the synergy 1 and 3. Besides, the P-values are also very close to each other, making it difficult to confirm if the changes for the 5 subjects in severe group are significant or not. Therefore, we cannot confirm that synergy 4 got worsen during the session. Another possible explanation for this reverse changes can be related to the level of the complexity in synergy 4. Synergy 4 was a combination of elbow extensor and shoulder related synergies. It is possible that SR has reverse effect on complex synergies and should be utilized during simpler tasks in individuals with severe stroke. The synergy improvements observed in this study has happened during simple synergies (synergy 1 and synergy 3) for severe group. Synergy 2 -which was more complex than synergy 1 and 3 and is less complex than synergy 4- did not show any changes. More investigation with more subjects is suggested to evaluate the impact of synergy complexity on the synergy changes during a SR training session.

Synergy 2 for the mild group showed the opposite behavior than other synergies. The mild group had the similar synergies to the control group at the beginning for all four synergies, meaning that they did not need further improvement. The reverse changes in synergy 2 for this group would indicate that not only SR was not beneficial to this group, but also it was even impairing their already normal elbow related synergy. This abnormality appeared as an inappropriate AD synergy added to their elbow related synergy at the end of the session. This can be a result of flexor muscle activations during the startle [25]. However, there is no clear evidence to explain why stimulating the brainstem in mild group would impair the elbow related synergy and there should be more studies for the mild group.

4.5.4 Mechanisms Underlying Muscle Synergy Changes

There are different potential mechanisms proposed for explaining mechanism of SR altering the movement and muscle synergies: 1) releasing the muscle spasticity by more activation of the muscles and 2) neuroplasticity changes resulted from triggering the brainstem and releasing the planed movement. The injury to the cortex in iwS causes changes in movement strategy (McCrea et al. 2005) by

reducing the dependence on the cortex and shifting it to lower parts of the brain (e.g. spinal and brainstem circuits) (Colebatch 1990). This study shows that SR might tend to alter the structures in the lower part of the brain and release a closer synergy to normal strategy for reaching movement in individuals with severe stroke. The improvements seen in muscle synergies are in favor of the second theory, since changes in muscle synergy means changes in central nervous system programming of the movement. Therefore, presenting SR during training may act as an endogenous stimulation of the brainstem circuitry, encouraging neuroplasticity to drive the use of this preserved structure in individuals with severe stroke. This brainstem stimulation is useless in individuals with mild stroke. In these individuals, the shift from the cortex to the lower parts of the brain is much less than individuals with severe stroke. Therefore, stimulating the lower parts of the brain is either useless (synergy 1,3 & 4) or even damaging (synergy 2).

4.5.5 Rehabilitation

The results of this study are consistent with the enhancements in movements and EMG data shown in our previous study (chapter 3). The enhancement of muscle synergy in severe group indicates that the abnormal flexor activity –which is exacerbated during SR trials in this group [18], [25] (chapter 1)- will not impair the muscle synergy of the voluntary movements. Contrarily, the abnormalities at the beginning of the session are lessened for individuals with severe stroke. This indicates that a session of SR exposure is in fact beneficial for iwS with severe impairment voluntary movement. This result is the opposite of the previous MSA reaching study, which shows voluntary arm reaching movements in individuals with subacute stroke is impaired with abnormalities, such as increase in activation of PEC and decrease in activation of TRI during [108].

The SR session has decreased the flexor activities in BR during shoulder horizontal adduction and the abnormal TRI activity in elbow flexor synergy in individuals with severe stroke. The abnormal BR and TRI activation at the beginning of the session can be a compensatory approach to control the elbow joint movement during reaching task in these individuals. Especially, BR is one of the elbow flexor muscles contributing the abnormal flexor activities in these individuals. According to Ellis et. al improving the flexion synergy is a better strategy than targeting the spasticity to improve arm function in iwS with

spasticity [79]. Therefore, SR is a better strategy for therapy for individuals with spasticity who are mainly the individuals with severe and moderate impairments. SR did not alter the shoulder joint muscles (AD, PD) as much as elbow joint, recomending the use of SR in elbow control rehabilitation.

4.6 Conclusion

This study addressed the concerns about the impact of elevated abnormal flexor activities during SR trials on the voluntary initiated movements in individuals with severe and moderate impairments. The results showed that startle point-to-point reaching session enhances the muscle synergies in these groups of iwS.

For future studies, comparison between SR and voluntary muscle synergy is recommended. This comparison can bring more information about the mechanisms of SR and abnormal flexion synergy existing during SR trials in individuals with stroke. Another suggestion for future study would be replacing the current task with a 3D with gravity point-to-point reaching task. Recent studies has shown larger differences between individuals with severe stroke and unimpaired individuals muscle synergy when there is no arm support against gravity [72], [81].

CHAPTER 5

5 CONCLUSIONS

5.1 Summary

This dissertation aimed to evaluate the effectiveness of SR as a new potential therapy for upper extremity of individuals with stroke. Despite the inappropriate flexor muscle activation during SR trials, SR did not impair the voluntary-initiated movement, muscle activities and muscle synergies after exposure to SR. Contrarily, SR was effective during SR multi-jointed movements and during voluntary-initiated movements after exposure to SR for iwS with higher impairments; the distance traveled and EMG activations were enhanced during SR trials (chapter 2) and the distance, accuracy, muscle activities and muscle synergies were enhanced during voluntary-initiated movement after exposure to SR (chapter 3 & 4). Specifically, the data in chapter 2 showed that a multi-jointed point-to-point reaching task is susceptible to SR and the percentage of muscle activation, EMG amplitude are larger and EMG and movement onsets are faster during SR trials in iwS. In addition, the distance traveled during SR trials were farther in individuals with moderate and severe stroke. In chapter 3, the data showed that the distance travelled, displacement and final point accuracies are increased and the EMG and movement onsets are decreased during the voluntary-initiated trials after exposure to SR for individuals with moderate and severe stroke. In the same chapter, we showed decrease in flexor muscles EMG amplitude and increase in extensor muscle EMG amplitude during elbow extension task after exposure to SR for individuals with severe and moderate stroke. Finally, in chapter 4, we showed alterations in 3 out of 4 muscle synergies during voluntary-initiated movements from the beginning to the end of the session. 2 of these alterations were matched with the movement changes in individuals with severe stroke, i.e. the similarity to the norm synergy indices increased to significantly not different to the norm synergy for 2 out of 4 synergies of the individuals with severe stroke.

5.2 Impact of This Study

This dissertation adds to the literature in favor of using SR in therapy. The enhancements in movement, muscle activity and muscle synergies mentioned above suggests that SR is safe for further

therapy studies with longer and more sessions of SAS. In addition to safe, SR is very low-cost comparing to other therapy methods. SR can be added to the training sessions by just producing a loud startling acoustic stimulus. The cost of purchasing a system to provide this sound is negligible compared to the cost of the available therapies. Besides, SR can be evoked by sounds as loud as 115 dB, during 0.01s with 2ms rising time, which is much shorter and less loud than a rock concert (2 to 3 hours of almost constant 120dB sound). Functional electrical stimulation (FES) is a new approach for activating the paralyzed muscles aimed to decrease spasticity and modify the muscle synergy [89]. This study showed that SR also has the ability to modify the muscle synergy. Compared to FES, addition of SAS is more natural and noninvasive. Therefore, SR provides us a low-cost, non-invasive and safe tool for future studies to enhance therapy outcomes.

This study emphasized that the most impact of SR has been on iwS with high impairment. Recent studies has shown that if the corticospinal tract has significant damage, recovery is poor[109], [110] and recent reviews highlighted that most new intervention strategies fail to benefit individuals with severe stroke likely due to the presence of large corticospinal damage in this population[110]–[112]. Training with SR represent a method to prime the nervous system to engage the more preserved structures (e.g. brainstem) in iwS with high impairment. SR induces neuroplastic changes in the brainstem as a useful rehabilitation target for individuals with severe stroke who had fewer options but needed the most recovery.

5.3 Future Directions

This study is the beginning of using SR in therapy and will encourage more research and investigation in this area. There are still more gaps in the SR literature that should be investigated before using SR in therapy. IwS have abnormal shoulder and elbow muscle synergies to compensate for the load of their arm during 3D point-to-point reaching task with no gravity support [96], [113], [114]. Future studies should evaluate the effectiveness of SR during more complicated and functional movements such as arm movements with no gravity support. In addition, SR has been investigated in single-jointed movements in lower extremity mainly [24]. This dissertation suggest expanding the studies evaluating SR multi-jointed lower limb movements, especially evaluating SR walking in iwS.

We need to confirm the impact of SR by a control cross-over study (no SAS control session) before performing clinical trials. This dissertation showed that it is safe to expose iwS to SR. Therefore, future studies can evaluate SR training by exposing iwS to SR during several sessions and complete a randomized cross-over control study. Contrary to the results presented for a SR session, we predict that the control session (session with no SAS trials) will impair the iwS's performances because of tiredness. In addition, the long-term effect of SR on iwS movement is unknown. It is important to measure the retention of SR therapy and evaluate the effectiveness or possible drawbacks of SR for longer period.

This study brings evidence to support that SR creates neouroplastic (the ability of neural networks in the brain to change through growth and reorganization) changes to improve muscle synergy and consequently the movement. However, to confirm this hypothesis and understand the exact alterations in the brain happening after exposure to SR, neuroimaging methods are necessary. EEG, TMS and fMRI tests are suggested to be performed before and after several sessions of SR training to measure any alterations in the brain.

We suggest studying SR during other rehabilitation approaches. Robot-assisted technology [7], [115]–[117] and task-specific training [2], [7], [85], [94], [118], [119] in therapy are recently studied by numerous groups. If SR impact these types of therapies in the same way as point-to-point reaching task, iwS with severe impairment can benefit from acceleration in recovery during their rehabilitation.

This study was not designed to measure the alterations before and after the SR session originally. There were 135 trials per arm in this study. The number of trials before and after the test trials were only 45 (= 10 voluntary + 5 SAS trials to each target) trials and the test trials (first and last 45 trials) were contaminated with SAS trials. In future, the test trials should be separated from the main training part and the training trials should be as many as possible (considering the time and tiredness limitations) to produce the maximum effect. Moreover, the SAS trials should not be among the test trials to make sure there is no SR effect during voluntary-initiated trials.

Finally, in this study we used SAS as loud as 115dB and collected data from only 20 iwS. In future studies, we advise to use louder SAS (>120dB) to make sure the number of SR trials (SCM+%) is maximum and we advise having at least 10 participants in each group of iwS (severe, moderate and mild)

to provide more significance in some of the results. We also advice assessing more clinical tests, including self-reporting questionnaires before and after each session and measuring more metrics such as the position, angle, force and torque of each joint as a function of time to provide more understanding about the impact of SR on each aspect of movement.

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