AN INVESTIGATION INTO THE STARTREACT EFFECT IN CHRONIC STROKE SURVIVORS

A thesis submitted for the degree of Doctor of Philosophy

By

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Letter to Examiners

The following thesis spans the years of 2019-2023. This is a longer time than the standard 3 years to complete a PhD thesis, but this was due to the Covid-19 pandemic. For a significant amount of time, I was unable to be in the lab to complete my studies which involved contact with human participants who were considered in the vulnerable group. Due to governmental restrictions during the pandemic, a total time of 19 months was missed in the lab. The time being from the beginning of the pandemic in March 2020 and the time when Brunel University London allowed human research in October 2021. On top of that, several other limiting factors came from the restrictions such as: expired equipment, equipment needing upgrades, and ethical approval extensions. Also, the recruitment group, who were based on campus, did not start back immediately, therefore recruitment could not commence until 2022 when they returned to group meetings. All limiting the amount of work that could be done towards the completion of my thesis.

During the pandemic it was unclear how long the stay-at-home order would last. Especially during the summer months when the stay-at-home order was lifted, but human research was not yet allowed. It was during this time I explored the possibility of taking a period of abeyance, but I decided against it due to the government guidance looking like it was going to open back up. In February 2021, the roadmap to lifting lockdown was announced, but in-person research was only allowed in October 2021. I was able to slowly begin working again, but the prolonged period away from the lab made it impossible to complete in a 3-year time period.

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This thesis has not been an easy nor quick process. It was riddled with complications throughout the entire journey from methodological hitches to a worldwide pandemic. Sometimes, it felt as if it would never be finished, but through the support of those around me, those feelings never lingered.

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Abstract

Stroke is one of the leading causes of movement disability in adults globally. The amount of motor disability after a stroke has been correlated to the amount of corticospinal tract damage, which is the major motor pathway damaged following stroke. A notion to improve motor function in stroke survivors is to employ alternate motor fibers, such as the reticulospinal tract (RetST), which may be spared after stroke. RetST originates from the brainstem and terminates at different levels of the spinal cord in the vicinity of motoneurons which opens the possibility of its use in rehabilitation. Prior to any attempt to use RetST in stroke rehabilitation, however, it is important to establish whether RetST could be triggered in stroke survivors non-invasively, and then assess its potential benefits in improving function.

One way of targeting the RetST is to use a "StartReact" protocol to foster early release of a pre-planned movement in response to a startling stimulus, suggested to be conveyed via this pathway. The ultimate aim in the current series of doctoral studies was to evaluate the feasibility of using “StartReact” experimental context for stroke rehabilitation. To this end, three studies were completed.

The first study was a systematic review with meta-analysis on the ability of a startling stimulus to shorten premotor time (PMT) (“StartReact” phenomenon) in stroke survivors. This study, published in Journal of Neurophysiology (DeLuca et al., 2022), established preservation of “StartReact” phenomenon in stroke survivors using published literature. The second study aimed to identify optimal experimental parameters for facilitating “StartReact” phenomenon in stroke survivors. In a “StartReact” experimental context involving a button press, it was determined in stroke survivors if there was an effect (pre-pulse inhibition or pre-pulse facilitation) on PMT by the ‘warning’ cue being delivered at specific predetermined time (interstimulus interval, ISI) before the ‘go’ cue. Results showed that employed ISI in the range of (50 – 2400 ms) did not have any inhibitory or facilitatory effect on the presentation of

“StartReact” phenomenon, and hence could be used in the third and final study. The third study sought to understand kinematic changes during execution of unconstrained discrete goal-directed motor tasks in a “StartReact” experimental context in stroke survivors. Results showed an increase in endpoint accuracy and a kinematic change in joint coordination between the elbow and wrist. The results, show that “StartReact” is a potential method for rehabilitation in stroke survivors and it has further potential to improve functional impairment by promoting changes in movement patterns. Future studies should look to explore the kinematic changes in a larger stroke population.

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List of Abbreviations

CST	Corticospinal Tract
RST	Rubrospinal Tract
RetST	Reticulospinal Tract
TMS	Transcranial Magnetic Stimulation
DTI	Diffusion Tensor Imaging
fMRI	Functional Magnetic Resonance Imaging
EMG	Electromyography
APR	Automatic postural response
PPI	Prepulse inhibition
PPF	Prepulse facilitation
MRC	Medical Research Council
DST	Dynamical Systems Theory
UCM	Uncontrolled Manifold Hypothesis
GMPT	Generalized Motor Program Theory
SD	Standard deviation
ApEn	Approximate Entropy
AMF	Alternate Motor Fibers
RT	Reaction time
PMT	Premotor time
SCM	Sternocleidomastoid Muscle
OOC	Orbicularis Oculi Muscle
PICO	Population, Intervention, Comparison, Outcome
sEMG	Surface Electromyography
ROB	Risk of bias
CI	Confidence interval
LAS	Loud auditory stimulus
CRP	Continuous Relative Phase
WGS	Warning + Go + Stimulus
WG	Warning + Go
ID	Index of Difficulty
ROM	Range of motion
AVE	Adjusted variable error

Chapter I Introduction

1.1 Stroke and Neuroplasticity

Stroke accounts for approximately half of all severe disabilities in adults (Stinear et al., 2007; Ward, 2011) and is shown to have a significant impact on the health and economy in many countries globally (Langhorne et al., 2011; Thrift et al., 2017). In the United Kingdom (UK), 84% of stroke survivors will require help with daily activities after being released from the hospital (SSNAP - CCG/LHB/LCG 2018; Stroke Association, 2018). In a survey by the Stroke Association of 1000 stroke survivors, it was reported that physical impact was the hardest disability to live with in 4 of 10 survivors (Stroke Association, 2016). The Stroke Association has developed a list of statistics concerning the UK which was published in its State of the Nation report (2018). Several statistics from this report displaying scale of the stroke impact on the society are summarized below:

- There are more than 100,000 strokes per year, and more than 1.2 million stroke survivors.
- Stroke is the fourth leading cause of death in the UK, and second leading cause of death globally.
- Strokes affect both adults and children; 400 children have a stroke every year.
- Approximately two thirds of stroke survivors leave the hospital with a disability.
- The cost of stroke to society is £26 billion a year.
- In the next 20 years, first time strokes in ages 45 and over, is estimated to increase by 59% and the number of survivors is estimated to rise by 123%.

With the increasing number of people surviving a stroke (Feigin et al., 2022), there is an increasing need for the development of new rehabilitative methods that improve functional mobility. In the UK, the percentage of stroke survivors living with upper limb weakness is 77%, and the percentage of individuals living with lower limb weakness is 72% (Stroke Association, 2016). Having reduced limb function takes a severe toll on an individual's daily activities. Most stroke survivors will always have a disability, and only 25% of patients regain the ability to participate in everyday activities with typical levels of function (Dobkin, 2005). In particular, upper limb dysfunction has a direct impact on the amount of participation in daily activities, whether functional or for leisure (Morris et al., 2013). Not all rehabilitation methods will work on every person, and progress will depend on the type and severity of the stroke (Dobkin, 2005).

After a stroke, the brain attempts to reorganize itself by forming new neural connections between different areas, in addition to maintaining neural pathways that have escaped injury. In this process, the main motor pathways connecting the motor cortex to the spinal cord would try to regain control and solve problems of movement while other pathways may get more engaged and/or compensatory movements adopted (Lemon, 2008; Ward, 2011). The reorganization that occurs will have a strong dependence on the extent and location of the damage (Schaechter, 2008). Neural reorganization after stroke will not be as effective as neuroplasticity of an undamaged brain (e.g., in learning new motor tasks), but it will be the best way the brain can adapt to the damage (Ward, 2011). Reorganization can be affected by several factors, such as treatment regimes, genetic status, and age. Imaging in animals and humans has given us a greater understanding of the way the brain changes after an infarct, and the reorganization process. Both animal and human studies are important in this regard, because together they provide a vivid picture of cerebral function and reorganization (Ward, 2011). The work by Lawrence and Kuypers in (1968a & b) allowed for a basic understanding of the reorganization in major descending pathways and was fundamental to future work in this area.

Descending pathways of the central nervous system permit commands originated in the brain to be transmitted to spinal motoneurons (Baker, 2011; Lawrence & Kuypers, 1968b). Descending pathways involved in the control of movement primarily consist of pathways that originate in the cerebral cortex (cortical) and pathways that originate below the cerebral cortex, such as the brainstem (subcortical). The descending pathways that originate in the cortex are the corticospinal tract (CST) and the corticobulbar tract. CST is the most important pathway for human voluntary motor control. The two cortical pathways are also known as the pyramidal tracts (Rea, 2015). The descending pathways that originate in the brainstem are separated into two groups based on where they terminate in the spinal cord (Lawrence & Kuypers, 1968a; Lemon et al., 2012). The two groups consist of the medial and lateral systems. The medial system, pertaining to the intersitiospinal tract, tectospinal tract, vestibulospinal tract, and reticulospinal tract (RetST), has termination points in the ventromedial part of the intermediate zone of the spinal cord gray matter (Lemon, 2008; Lemon et al., 2012). The lateral system, pertaining to the rubrospinal tract (RST) and pontospinal tract, has termination points in the dorsal and lateral areas of the intermediate zone (Lemon, 2008; Lemon et al., 2012). Individual descending pathways control movement in various ways. Although CST is the most important pathway in human motor control, alternate motor pathways may need to be considered to regain function after damage to the CST which commonly occurs in stroke.

The RetST is known to have some control over posture, locomotion, reaching, and proximal and distal control over the limbs (Baker et al., 2015; Lemon, 2008; Lemon et al., 2012, Riddle et al., 2009). The RetST may work synonymously with the CST, due to their termination points being in the same areas, but the RetST projections are not as specific as the CST (Baker, 2011; Riddle et al., 2009). The RetST has been studied in animals such as monkeys and rodents, but in humans the method of studying the RetST is through the use of a startling stimulus. Such an approach has been adopted by investigators examining StartReact phenomenon in both non-clinical and clinical populations.

In a StartReact experiment, a startling stimulus (usually a loud acoustic noise) is unexpectedly delivered while the participant is waiting to execute a movement in response to a non-startling stimulus (Carlsen et al., 2012; Honeycutt & Perreault, 2012; Valls-Sole, 1995). StartReact is known to release a preprogrammed movement faster than when there is no stimulus (Carlsen et al., 2004a, 2004b; Honeycutt et al. 2013). The time between the onset of the startling stimulus and the onset of muscle activity is known as premotor time (PMT). PMT in StartReact has been extensively studied in clinical and non-clinical populations. Both populations showed a quicker PMT when a startling stimulus was delivered in conjunction with the 'go' stimulus. The PMT measured in a StartReact experiment are believed to be mediated through the RetST. This is partly due to classic startle reflex literature where the startle reflex is known to be mediated through reticular structures and partly due to the amount of time needed to have cortical involvement (Carlsen & Maslovat, 2019, Valls-sole, 1995).

StartReact in the stroke population has been studied in upper limb movements, speech, and postural control (Choudhury et al., 2019; Swann et al., 2022; Yang et al., 2019), with the majority of the studies being on upper limb movements. From the studies on StartReact it is known the RetST is intact after a stroke, chronic stroke survivors motor programming ability is intact, but it is believed the kinematic measures of the movement remains unchanged (Carlsen & Maslovat, 2019). The findings implicate StartReact as a potential to be a tool in clinical rehabilitation.

Largely the studies done on upper limb movement in StartReact are performed on single joint movements where other elements of the body (trunk movement) were constrained (Ossanna et al., 2018). More recent studies have progressed to multi-joint upper limb movements, but the movement still contains some constraints such as limited trunk movement (Ossanna et al., 2018). Outcome measures of upper limb movements are measures such as endpoint accuracy, PMT, displacement RT, angular displacement and velocity, and movement time (Carlsen et al., 2004a; Honeycutt et al., 2014;

Ossanna et al., 2018). The results from these studies give a 2D viewpoint on Kinematic changes in StartReact and highlight the need for an analysis that evaluates the inter-joint coordination patterns that are present in startle trials.

1.2 Thesis Overview

A series of three studies were developed from existing literature in StartReact. Published literature has various methodologies which informed development of the current thesis methodology. Existing literature uses two cues to create a StartReact experiment: the first cue will be identified in this thesis as the 'warning' cue. The participant is instructed to prepare to execute the movement when this cue is delivered. This cue is the first cue to be given to the participant and some studies refer to this cue as a 'prepulse'. The second cue presented to the participant is the 'go' cue. This cue is delivered at a predetermined time after the 'warning' cue and the participants are instructed to execute the movement when this cue occurs. The final element to the StartReact methodology paradigm is the startling stimulus (startle), usually a loud auditory stimulus (LAS). The LAS is paired with the 'go' cue in trials randomly interspersed among regular trials to prevent anticipation and limit habituation of the startle. Participants are not instructed on how to react to the stimulus and to continue to respond to the 'go' cue as instructed.

In a StartReact experiment, a startling stimulus accelerates RT which is seen in the participants' PMT component of the executed movement and is believed to be mediated through the RetST. The theory of RetST involvement, which can be seen as an alternative pathway to carry motor commands, led to developing the aim of the current thesis which was to evaluate the feasibility of using alternate motor fibers in stroke rehabilitation using StartReact experimental context.

The following chapters of this thesis support the notion on the potential usefulness of StartReact experimental context for motor rehabilitation after stroke. Chapter 2 is a review of current

literature that pertains to the potential use of StartReact in rehabilitation. Chapter 3, the first study, is a systematic review with a meta-analysis to support evidence for the preservation of StartReact phenomenon in stroke survivors. Chapter 4, the second study, is an experimental study establishing the appropriate interstimulus interval (ISI) for future protocols which may use StartReact. Chapter 5, the third study, is determining kinematic changes in a reaching movement under a StartReact protocol which support the potential benefit of training stroke survivors in a StartReact context for motor rehabilitation. Chapter 6, the general discussion, is summing up the findings of each study.

1.2.1 *Systematic Review with a meta-analysis – study 1.*

The first investigation was a systematic review with a meta-analysis on the ability of StartReact to shorten PMT and to justify the use of StartReact protocols after stroke from published literature. Due to StartReact being a relatively new area of research published literature on the topic is scarce and there are multiple populations used in the methodologies. The first investigation was to pool together published literature in StartReact in the stroke population. The results from this study impact the current thesis by clarifying the amount of research done in the area, distinguishing the current methodologies used and their differences, and determining if PMT enhancement is seen in the stroke population.

The literature was systematically searched, and six studies were included in the meta-analysis. The number of qualified studies in the systematic review indicated a lack of literature on StartReact effect in individuals who have had a stroke. From the included studies a total of 151 clinical and non-clinical participants data was included. Results supported the preservation of StartReact effect in stroke survivors and highlighted the need for a more consistent methodology in StartReact experiments.

The systematic review also gave the author of this thesis background knowledge of how to build the methodology for later studies used in this thesis. In particular the sound level, movements used, EMG locations, implementing a measure of startle, and interstimulus interval (ISI) times.

1.2.2 *Prepulse inhibition/prepulse facilitation – study 2*

The second investigation was the first experimental design of this thesis. The aim of the second study was to determine if there was an effect on premotor time by the 'warning' cue being delivered at a predetermined time before the 'go' cue in stroke survivors. This is known in the literature as prepulse effect (prepulse inhibition and prepulse facilitation). As stated below, prepulse inhibition (PPI) and prepulse facilitation (PPF) have been extensively looked at in clinical and non-clinical literature; however, it has not been researched in individuals who have had a stroke.

PPI and PPF are increases/decreases in the amplitude of a startle response as a result of the time the 'warning' cue (prepulse) is given (Aasen et al., 2005; Maslovat et al., 2012). PPI/PPF come from the startle reflex literature and is usually measured by activation seen in the sternocleidomastoid muscle (SCM) or orbicularis oculi muscle (OOC) within 120 ms of the LAS. Research into the effects of the prepulse and the startle reflex are primarily in psychiatric disorders such as Schizophrenia, Huntington's disease, Tourette's, and Parkinson's disease (Fendt et al., 2001; Maslovat et al., 2012). Whether a prepulse has an inhibition effect or a facilitation effect relies heavily on the ISI time, duration, frequency, and intensity of the prepulse (Gómez-Nieto et al., 2020).

In creating a methodology for future studies that have an ISI time it is important to understand what the effect the ISI time has on the outcome measures in the study. In the case of this thesis, determining if the ISI time had an effect on the PMT recorded was needed. The startle reflex literature in humans suggests PPI is seen between 40 – 150 ms, and PPF is seen with ISI times of greater than 500 ms (Aasen et al., 2005; Fendt et al., 2001; Maslovat et al., 2012; Gómez-Nieto et al., 2020). PPI and PPF have been studied in the startle reflex literature, but only once to this author's knowledge in the StartReact literature and the population was non-clinical. It was necessary to use StartReact in a stroke population to establish the ISI time used in future protocols.

An experimental design was used to measure the effect of the ISI on PMT. In a StartReact experiment, outlined in detail in Chapter 4, participants were asked to complete a button press task as quickly as possible. Each trial consisted of a different ISI time. Some ISI used are known to inhibit the startle reflex and some are known to facilitate the startle reflex. EMG activity on the extensors and flexors of the wrist were taken as a measurement of PMT and EMG activity of the SCM was taken as a measure of startle. SCM activity as a measure of startle is commonly distinguished in the literature as SCM+ or SCM-. In the results of Chapter 4 all PMT recorded were included in data analysis due to this author's belief that StartReact was elicited in the experiment. A full explanation is provided in Chapter 4.

This experimental study gave the thesis a working methodology for a future experimental study, an indication of which ISI could be used, and further data to show quicker PMT when a LAS is delivered. This information was used for the third and final study of this thesis.

1.2.3 ***Kinematic change and endpoint accuracy – study 3***

After a stroke, movement of the upper limb (e.g., synergy formed between upper limb segments/joints in moving toward a target) can be described as rigid (or less flexible and stereotyped represented by reduced variability) while associated with increased end-effector variability (Stergiou et al. 2006). Accordingly, increasing movement variability which may be associated with improved endpoint accuracy could be the purpose of rehabilitative interventions.

Kinematic movement analysis is needed in a stroke population to determine if StartReact can be used to improve function. Current analysis in StartReact largely consists of single joint movements with only a few multi-joint movement studies and report there is no kinematic change when a startle is involved. This is reported from outcomes of movement patterns rather than an analysis at the joint level such as is completed in the results section of Chapter 5.

The third experimental study of this thesis sought to understand kinematic changes during execution of goal-directed motor tasks in a StartReact experimental context in stroke survivors through

the use of a motion analysis system. Participants completed an unconstrained reaching task in a StartReact experimental study. Endpoint accuracy, coordination, and PMT measures were taken during the movement. This study further elucidates the notion of StartReact to be used in rehabilitation. It also highlights areas of methodology to be further analyzed and provides direction for further research.

Chapter II Literature Review

2.1 Descending Pathways for Motor Control

2.1.1 Corticospinal Tract

The CST is the leading descending pathway for motor control in humans (Baker et al., 2015; Lemon, 2008). In all mammals the CST exists but it is used in different ways (Lemon, 2008). In humans the CST termination points overlap with the termination points of both the lateral and medial pathways (Lemon, 2008). The CST originates from many areas of the cortex and has termination points distributed within the grey matter of the spinal cord (Lemon, 2008). In the CST 30–40% of axons originate from the primary motor cortex. The remaining origination points of the CST are from the premotor and supplementary motor cortices, and in parietal areas (Rizzolatti et al., 2014). The multiple origination points and termination points lead investigators to believe that the CST is not limited in what it controls and is multifunctional (Lemon, 2008). Voluntary movements, especially isolated control of the hand and fingers, are under direct control of the CST. Termination points of the CST occur throughout the whole of the spinal cord, but they are seen most in the areas of the spinal cord that control the distal muscles in the limbs (Rothwell, 2012).

According to where the location of the origination point is an assumption of functional ability can be made (Jang, 2014; Lemon & Griffiths, 2005). Examples include: an origination in the primary motor cortex, i.e. M1, would be beneficial in movement execution, origination in the premotor cortex would be beneficial in the sensory guided movements, origination in the supplementary motor area would be beneficial in internally generated movement, and an origination point in the somatosensory cortex would be beneficial in the descending control of afferent inputs (Jang, 2014; Lemon & Griffiths,

2005). Different origination sites also contribute to the CST being separated into three CST: the lateral crossed CST, the lateral uncrossed CST, and the anterior uncrossed CST. Each of these sections have their own set of functions, but the exact functions of the individual CST are not clear in the current research (Jang, 2014). Researchers use what they already know about the functions of the CST in rehabilitative practices, but there are still many functions that are unknown and need to be explored.

The CST is known to have significance in the control of the hand particularly in individual finger movements (Baker, 2011; Zaaimi et al., 2012). The ability of the CST to trigger individual muscles of the fingers is exclusive to the CST, whereas other descending tracts have widespread output that is not selective enough to control fine finger movements (Honeycutt et al., 2013; Zaaimi et al., 2012). The CST projections that reach the fingers are less distributed, and stronger than other descending tracts (Honeycutt et al., 2013). CST monosynaptic connections are particularly important for control of finger movements. Other connections include synapses with interneurons that are significant in the control of larger muscles (lemon, 2008). One of the key studies into the motor systems done by Lawrence and Kuypers (1968b) demonstrated that after a complete lesion to the CST, Rhesus Monkeys lost control of individual finger movements; a discovery that has been seen in multiple studies since. Lawrence and Kuypers' study used 41 monkeys to study the motor behavior after a complete lesion to the pyramidal tract. Not all lesions were only contained within the pyramidal tract and affected other brainstem pathways demonstrating that each pathway has different influences in motor control. However, 8 monkeys only had a lesion to the pyramidal tract. These monkeys were able to produce locomotion but were incapable of using their hands and upper limbs without total body movements. The monkeys were also incapable of picking up small pieces of food but could grab their cages. They determined that the monkeys lost singular control of the digits after the lesion to the pyramidal tract. This is in line with recent research that also shows after a CST lesion, individual finger movements are severely affected.

With the CST being the main pathway for motor control, when there is damage done, there can be a significant amount of impairment in an individual's usual movements. In fact, some studies claim that the amount of CST damage correlates with the amount of functional recovery (Lin et al., 2019; Stinear et al., 2007) after injury to the brain. CST damage can be assessed by techniques, such as transcranial magnetic stimulation (TMS), diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI). Stinear et al. (2007) completed a study that aimed to predict the amount of functional improvement in chronic stroke survivors. They examined 17 chronic stroke patients before and after a 30-day motor practice program. They used TMS, DTI, and fMRI as neurophysiological methods to determine CST integrity, and the fugl-meyer scale and the National Institutes of Health Stroke Scale to assess the participant's impairments. A change in the fugl-meyer score after the motor program was used as a marker of functional potential. Lin et al. (2019) further looked into predicting motor recovery of the upper limb depending on the CST damage. Authors note that previous investigations have shown that upper arm recovery is dependent on the amount of CST damage done from the stroke, but the amount of damage has yet to be used to predict the amount of recovery.

Lin et al. (2019) completed a similar study to Stinear et al. (2017) in which they used the fugl-meyer assessment and imaging techniques such as fMRI and DTI, but differed in they investigated the acute phase of stroke rather than chronic stroke survivors. Investigators had 48 participants and found the participants who (as labeled in the study) proportionally recovered and participants with limited recovery were separated into groups by what extent of damage was done to the CST by the stroke. This study is enlightening because it reiterates what previous literature has suggested that motor recovery can be estimated by the damage done to the CST, but it also demonstrates that this can be done by imaging techniques that are already a part of the standard of care. The measurements used in analysis were from scans that were taken in the hospital when the patient was admitted. The importance of

using images that are a part of the standard of care is there is a repeatable method that can be used in future studies and clinicians can use information they already have to guide patient care.

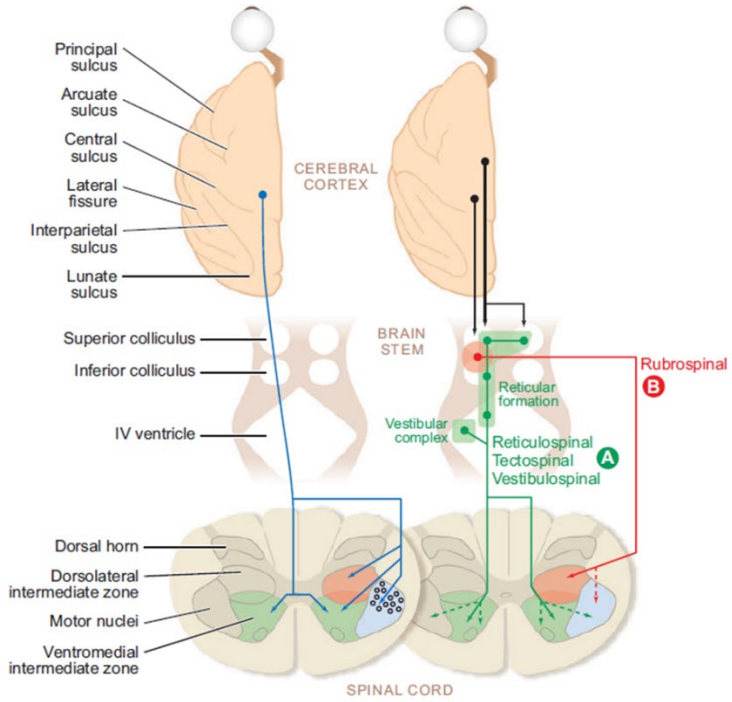
The results from both studies suggested that the amount of improvement after a stroke can be predicted by evaluating the CST integrity. They also reiterate that the amount of damage done to the CST correlates with the amount of functional impairment. The implications of these results are that methods of rehabilitation should be tailored to the individual, and specific strategies be used based on the CST integrity. In both studies the results demonstrate the importance of continuing research into rehabilitation methods after stroke. Including looking into AMF in cases where the CST has significant damage.

2.1.2 Rubrospinal Tract

The RST and CST have many similarities in the way they control movement, but their projection patterns onto motoneurons differ significantly (Kuchler et al.,2002). Figure 1 is from Lemon (2008), and it shows the descending pathways of the CST, and AMF.

Figure 1

Descending Pathways of the CST and AMF



Note. Descending pathways of the CST and AMF. The figure illustrates the descending pathways of the CST from the cortex, and the AMF from the brain stem. The termination points of all descending pathways are in the spinal cord. The AMF termination points are in the same areas as the CST. This shows the possibility of AMF as a potential method to compensate for lost motor control after damage to the CST. This Figure was published in Descending Pathways in Motor Control by Lemon (2008).

The RST is a descending pathway that originates from the magnocellular red nucleus located in the brainstem and terminates in the regions of the spinal cord, involved in control of the extremities, the lateral and dorsal region of the intermediate zone (Lemon, 2008; Lemon et al., 2012). The red nucleus is divided into magnocellular and parvocellular (Muir & Whishaw, 2000). The parvocellular part of the red nucleus directs the feedback that is received from the cerebral cortex to the inferior olivary nucleus and cerebellum (Muir & Whishaw, 2000). The magnocellular collects information from the

dentate and interpositus nuclei in the cerebellum and is the source of the rubrospinal projections (Muir & Whishaw, 2000). While the CST is used as a primary control pathway for almost all motor systems, increasingly the RST is being shown in animals to operate in compensatory manners after damage to the CST and maximize motor possibilities within recovery after damage caused by central nervous system lesions. Combining pathways from the RST and the CST the dorso-lateral pathway is formed and has major motor control implications for all extremities, and is particularly impactful on sensory pathways, and the distal (finer motor) portions of the limbs (Belhaj-Saïf & Cheney, 2000), including reach and grasp (Lawrence & Kuypers, 1968a).

The role of RST in the control of movement has been studied in rodents and monkeys, in fact most of what is known about the RST comes from animal research. In animals, RST role is usually considered more important for function in the forelimb over the hindlimb (Belhaj-Saïf & Cheney, 2000; Kuchler et al., 2002; Lawrence & Kuypers, 1968a; Lemon, 2008; Muir & Whishaw, 2000). Moreover, whether the RST has a propensity for extension or flexion movements is still a debate. Lemon (2008) suggests that the RST has more control over flexor muscles, while Belhaj-Saif and Cheney (2000) suggest that the RST has an inclination for extensor muscles. However, it is commonly thought that the RST aids in reorganization of motor output after there is damage to the CST. A study done by Belhaj-Saif and Cheney (2000) produced results that showed when there is damage done to the CST, the reorganization of the RST shows a more even contribution to the extensors and flexors during movement. The same study suggests that the magnocellular red nucleus is responsible for reorganization of function in the forelimbs after damage to the pyramidal tract. In this study three rhesus monkeys were taught a reach and grasp task. They were taught to have their hand on a start point, reach to grab food from a cylinder, bring the food to its mouth, and return the hand to the starting point. The output of the magnocellular red nucleus was measured using stimulus triggered averaging of electromyography (EMG) (electrodes located in the forearm muscles). Two monkeys were used as control monkeys. The third monkey was

five years post lesion of the pyramidal tract. The red nucleus output in this monkey showed an increase in even distribution between extensor and flexor motor output, in contrast with the control monkey data which demonstrated the red nucleus facilitates extensor movements more than flexor movements. This study was done to examine the reorganization capability of the red nucleus after the CST is lesioned. The chosen task was appropriate because a multi joint movement task showed the proximal and distal synergies that are important in functional movement. However, in the procedure to create the lesion, only 65% of the CST was damaged. This leaves a significant amount of the CST to aid in recovery post-operation. The deficits that remained with the monkey five years later was impairment in the digits. Functional use of the arm and hand were recovered. This is important because the study suggests they show reorganization of the red nucleus, but CST activity cannot be ruled out of being a contributor to the recovery due to how much of it was left undamaged. Also, their results showed the reorganization had a more even distribution to extensors and flexors in the lesioned monkey, and a more even distribution is characteristic of the CST rather than other pathways. The study showed a promising start to the research, but due to the limitation of having only one lesioned monkey and two control monkeys the results could be left up to interpretation.

The amount of evidence that suggests AMF (such as RST) have an influence in motor recovery in humans is small (Rüber et al., 2012; Schulz et al., 2017) with some authors arguing the RST is doubtful to have an impact after CST damage (Baker et al., 2015). However, in participants who have had a stroke, investigators from multiple studies have seen a correlation between the control of movement retained after stroke and microstructural changes to the red nucleus (Rüber et al., 2012; Schulz et al., 2017; Takenobu et al., 2014). The importance of these changes to functional recovery has not been studied (Takenobu et al., 2014). This evidence leads to the assumption that AMF have the potential to play a compensatory role in functional recovery post stroke (Rüber et al., 2012; Schulz et al., 2017). Schulz et al., (2017) suggests that the RST and the RetST are mostly independent of one another but have similar

importance in the recovery process after a stroke. If the importance of the two tracts are similar in motor control, conceivably both may be exploited in designing new rehabilitative techniques.

The next three studies all report similar findings regarding microstructural changes in the motor pathways following stroke, despite employing different techniques of DTI, tractography, and the measure fractional anisotropy in their respective investigations. It is important to note that while DTI can show microstructural changes it is not sensitive enough to differentiate between the AMF. This is important because there is not a way of reporting exactly what tracts (RST, RetST, or even other tracts) contribute to the observed results. The use of fractional anisotropy as a measurement of microstructural changes is a method that is not fully understood and is still being investigated. The results that are achieved using fractional anisotropy are consequently up to interpretation by researchers (Rüber et al., 2012).

In the study conducted by Schulz et al. (2017) the CST and AMF in subacute stroke survivors were monitored. Their aim was to assess the microstructural integrity of both the CST and AMF, and also to determine if AMF can be responsible for motor recovery. Their results showed that the structural states of both the CST and AMF correlated with motor recovery. This study recruited a large number of individuals with late subacute stroke. More research needs to be done on chronic and acute stroke survivors for a thorough understanding of possible microstructural changes during recovery from stroke. The study could also benefit from having information on how much of the CST was damaged from the stroke.

The next study was done by Ruber et al., (2012). This study aimed to show if there were structural differences in the CST and AMF between healthy participants and stroke survivors, and if the diffusivity in stroke survivors was related to their functional impairment. Their results showed a higher fractional anisotropy value surrounding the red nucleus in stroke survivors when compared with the

healthy participants. Their interpretation was that a higher value of fractional anisotropy was a sign of reorganization, and a lower value could mean degeneration of white matter. This led them to the interpretation that the RST, stemming from the red nucleus, aids in motor recovery after damage has been done to the CST. The study also refers to the AMF as crossed and uncrossed RST instead of RST and RetST. These results do stand out compared to Schulz et al. (2017) with the addition of healthy participants.

The third study, completed by Takenobu et al., (2014) was a longitudinal study that aimed to show if changes in microstructure over time was correlated with changes in motor recovery. Only 10 stroke survivors were used and had a male majority, subsequently the participants cannot be indicative of the overall stroke population. This study is different than the other two in the way that it took three scans over the course of three months instead of only one scan. The study found an increase in fractional anisotropy around the red nucleus and dorsal pons. They suggested the increases were indicators that the RST and the RetST aided in motor recovery post stroke. All three studies had stroke survivors with minor to moderate impairment levels. Further research needs to be done including the moderately severe and the severely impaired.

2.1.3 Reticulospinal Tract

As mentioned previously there is a lack in technology to accurately measure the descending pathways. Previous work on animals has helped establish current knowledge about the descending pathways. More recent work in tractography allows for a better picture of the pathways, but there is still a need for more sensitive imaging techniques.

RetST is one of the descending pathways that make up the ventromedial brainstem pathways. The RetST stems from the Reticular Formation located in the brainstem (Baker et al., 2015). RetST projections are believed to have terminal points that are dispersed within the spinal cord mainly in the

interneurons of the intermediate zones, and the motoneurons that innervate the limbs particularly in the proximal and axial regions (Riddle et al., 2009). Actions that have shown to be under some influence of the RetST are reaching, posture, and locomotion. Although the RetST does not have sole control over these actions. The literature points to the idea that the RetST and the CST work together in control of these movements (Baker, 2011). In a study done by Riddle & Baker (2010) interneurons of the intermediate zone were recorded in two monkeys. The CST and RetST were stimulated to see if the responses had any overlap. The results of this study showed that the interneurons of the intermediate zone receive input from both the CST and what they believe was the RetST. The area of stimulation for the RetST has other descending tracts, and the investigators cannot be completely sure it was only the RetST being stimulated. An occlusion test was done to determine when the RetST was being stimulated to establish the CST was not stimulated. The interneurons receiving input from the RetST in the same place as the CST shows that the RetST can produce similar motor control as the CST in Monkeys, but the study still has the limitation of not accurately establishing it is stimulating the RetST.

Recent studies in animals propose the RetST takes on a stronger role in voluntary motor control when damage has been done to the CST (Van Lith et al., 2018). Studies have used cats, rodents, monkeys, and lamprey to study the RetST functional role (Riddle et al., 2009). The predominant impression about the RetST is that it has an important role in locomotion, posture, and proximal control of the limbs (Baker et al., 2015; Lawrence & Kuypers, 1968a; Lemon, 2008; Lemon et al., 2012). However, Riddle et al., (2009) found in monkeys the RetST does reach the distal muscles leading to the wrist and the intrinsic muscles of the hand. This study used stimulation of the medial longitudinal fasciculus of the medulla that is known to have descending axons of the RetST in three monkeys. The stimulation was used to measure the responses from the RetST in the upper limb. This area of the medulla also contains other descending tracts, such as the vestibulospinal tract and the tectospinal tract. By using this area, it is a possibility that the researchers stimulated these tracts as well as the

RetST. There is not a method to discern which tract was stimulated. The same paper found the RetST has effects on the projections to distal muscles, particularly the intrinsic hand muscles, not only proximal muscles which is previously believed. The results showed that the RetST may work in parallel with the CST and have an influence on hand muscles, but it does not have as many projections that would control fine finger movements. This study, along with other studies performed on monkeys, find the same connections from the RetST to the distal muscles even though it is thought to be predominantly involved with control of the proximal muscles of the limbs (Baker, 2011; Riddle et al., 2009; Soteropoulos et al., 2012).

In a study done by Soteropoulos et al., (2012) data was collected from monkeys who were trained in an extension/flexion index finger movement task. The study found that delivering stimuli to the reticular formation could activate finger muscles. However, the functional impact of the connections is still uncertain, and it is not clear if the RetST can control the smaller muscle synergies (Soteropoulos et al., 2012).

The preliminary studies on animals give encouragement to the idea that the RetST is an alternate pathway that can be used when the CST is damaged. Another study supporting such view was conducted by Davidson and Buford (2006) on monkeys in which they investigated the bilateral control of the RetST. Their results showed that in the upper limb, on the contralateral side, the RetST enables extensors and suppresses flexors, and on the ipsilateral side the RetST enables flexors and suppresses extensors. This study, however, has the same limitations as previous ones done on monkeys, as the area of stimulation also contained other descending pathways.

Using literature on animals Honeycutt et al. (2013) looked to assess if the connections seen in monkeys can be found in humans. In their study a StartReact (thought to elicit RetST) protocol was used to assess the activity in two different tasks: an individual finger task and a grasp task. StartReact

experimentation is discussed in detail in section 2.2 below, but briefly is referred to experimental conditions during which a preplanned movement is executed involuntarily in response to an unexpected, startling stimulus. Experimentation in this context has been used to show voluntary movements could stem from subcortical regions. Honeycutt et al., (2013) used 17 unimpaired individuals to complete a task involving grasp using all fingers, and another involving movement of individual fingers. StartReact elicited the grasping response involving all fingers, but when the task was to move individual fingers StartReact did not elicit any response. Their results corroborate those found in monkeys showing the RetST does have connections to the hand, but it is unclear how much control it has over the fingers. In a separate study done by Honeycutt et al. (2015) the same StartReact effect was examined in hand extension in stroke survivors. They used the same StartReact methodology, but the task involved hand extension only. The idea that StartReact can elicit hand extension in both healthy individuals and stroke survivors is important because it demonstrates that the RetST does control the distal muscles of the limbs. Authors explained how their results showing the RetST being involved in the control of more distal portions of the forelimbs in humans add depth to the traditional views of the RetST.

2.2 StartReact/Startle Reflex

Regaining voluntary control of movement after a stroke is still a topic to be explored. There are several stages involved in the execution of a motor task, and both preparation and execution stages of a given movement may suffer after stroke. As suggested by Honeycutt and Perreault (2012), it is unknown if abnormal movement patterns observed after stroke are due to loss of voluntary control, or loss of being able to preplan a voluntary movement. The deficits in preplanning of movement patterns have been examined in multiple ways. These include the use of startle reflex and StartReact. Startle reflex and StartReact are interesting topics to explore because of their prospects in rehabilitation and diagnostic

aspects. Startling stimuli could prove to be useful in stroke rehabilitation due to its ability to trigger prepared actions (Castellote et al., 2017).

Startle reflex is an involuntary reaction by muscles to a startling stimulus (Honeycutt & Perreault, 2012). The startle reflex is believed to be a protective response to an attack (Dean & Baker, 2016; Yeomans & Frankland, 1996). The startle response is an automatic/reflexive response that can be used in animals and humans. This allows for comparative research (Grillon & Baas, 2003). Startle Reflex predominantly affects flexors over extensors but does form an adaptation over multiple trials (Honeycutt & Perreault, 2012). For measuring when the startle occurs, researchers tend to use one of two methods. One being a measurement of the eye blink response by monitoring electrical activity of the OOC muscle (Grillon & Baas, 2003) and the other a measurement of muscle activity in the SCM (Carlsen et al., 2004a). The startling stimulus that is commonly used is a loud acoustic stimulus, although other forms of stimulation can be somatosensory or vestibular (Castellote et al., 2017). The literature on the startle response in clinical and non-clinical populations has increased, and in particular is used as a cognitive measure for sensorimotor gating discussed below (Aasen et al., 2005). The literature that looks into the startle reflex began by using reaction time (RT) tests. The research showed that when a loud acoustic stimulus was used, the RT was shorter than when done voluntarily (Baker & Perez, 2017; Carlsen et al., 2012). However, startle reflex tends to have a high habituation effect on the participant (Yeomans & Frankland, 1996), and StartReact (below) does not exhibit the same habituation. Accordingly, it is hypothesized neural structures that mediate startle reflex and StartReact are different (Alibiglou & Mackinnon, 2012; Honeycutt & Perreault, 2012, 2014).

StartReact is the involuntary release of a preplanned movement triggered by an unexpected (usually) acoustic stimulus (Alibiglou & Mackinnon, 2012; Carlsen et al., 2012; Honeycutt & Perreault, 2012). It is speculated that the prepared action in StartReact is stored in subcortical structures (Carlsen

et al., 2012; Dean & Baker, 2016; Marinovic & Tresilian, 2016; Valls-Solé et al., 2008). The startling acoustic stimulus then excites these structures, and the pre-planned movement is released with a shorter latency compared to movements executed in response to the expected regular stimulus (Carlsen et al., 2012; Dean & Baker, 2016; Marinovic & Tresilian, 2016; Valls-Solé et al., 2008). It is suggested that StartReact responses stem from the reticular formation and the movements are executed through the RetST (Baker & Perez, 2017; Coppens et al., 2018; Dean & Baker, 2016; Honeycutt et al., 2013; Honeycutt & Perreault, 2012). StartReact has been suggested to be mediated via subcortical structures, as the latency of the responses are too short to support cortical involvement (Alibiglou & Mackinnon, 2012; J. Valls-Solé et al., 1995). Most of the evidence that leads researchers to the subcortical origin of StartReact responses is reliant on animal studies (Honeycutt et al., 2013; Riddle et al., 2009) and RT tests (Marinovic & Tresilian, 2016). As stated above, RT of movements released in response to a startling stimulus is shorter than when the movement is executed without the presence of the startling stimulus (Marinovic & Tresilian, 2016). The theory found further support by evidence that patients who suffer from Parkinson's disease have a slower StartReact response (Baker & Perez, 2017; Dean & Baker, 2016). Parkinson's disease is commonly known to be associated with impairment of the reticular formation (Baker & Perez, 2017; Dean & Baker, 2016).

Several studies have looked into the StartReact effect on planned movement since it was described by Valls-Sole et al. (1999). The theory that StartReact is a method of releasing stored motor preparation is still being researched. Coppens et al. (2018) investigated the effect StartReact had on lower limb movements (i.e., ankle dorsiflexion) and automatic postural responses (APR). APR is mediated via the brainstem, and it is common for APR to be impaired after stroke. When a startling stimulus was used in this study in association with balance perturbation, there was a faster APR response. This suggests that motor preparation might be intact after stroke and appropriate responses

may still be accessed via the brainstem, but the hindrance is in the release. The results added further data to show that StartReact can release a planned movement.

Honeycutt & Perreault (2012) aimed to establish if the StartReact effect is seen in stroke survivors. This study used impaired and unimpaired individuals. Each group had 10 participants. The Fugl-Meyer assessment was used to measure impairment and most participants were mild-moderately impaired. This is important because some studies have shown the StartReact effect to be different according to the level of impairment. Honeycutt & Perreault (2012) had their participants complete a single joint movement that consisted of elbow extension and flexion. Flexion synergy is commonly seen in stroke survivors, and it is considered an impairment that needs to be corrected. Having a movement that focuses only on extension would be important for future studies. In their results they found that in stroke survivors, both flexion and extension tasks, movements were executed as fast as the unimpaired individuals. This further shows that StartReact can be elicited in the stroke population. In the flexion tasks movements were executed similarly to the unimpaired individuals executed the movement. In extension trials, the task was inhibited by inappropriate activation of the flexor muscles. However, this inhibition did diminish in later trials. The inappropriate flexion activity led authors to the hypothesis that it is due to the incapability to suppress the classic startle reflex. Furthermore, the results of the study implicate the pathways needed to elicit StartReact in stroke survivors are intact and could potentially be used in rehabilitative methods.

Ossanna et al., (2018) expanded on the use of StartReact in single joint tasks and employed a multi-joint movement in unimpaired individuals. The results indicated StartReact can be evoked in multi-joint movements in multiple directions. Authors interpret the results as suggesting that StartReact can prompt a sophisticated motor plan that has the potential of being used in future clinical and non-clinical studies.

Evidence to support both the startle reflex and StartReact responses are often producible in individuals with injury to the CST such as Stroke (Honeycutt & Perreault, 2012) and Spinal Cord injury (Baker & Perez, 2017). Preliminary evidence proposes that individuals post-stroke plan more movements than they voluntarily can complete, and that StartReact pathways can be used to produce the targeted movement. Many papers have shown StartReact response (Coppens et al., 2018; Honeycutt & Perreault, 2012; Honeycutt et al., 2015) and startle reflex (Li et al., 2014) continue to be producible after stroke. Li et al. (2014) conducted a study to examine responses from startle reflex in chronic stroke patients in spastic and non-spastic stages. They used startle reflex in seventeen chronic stroke patients. Participants were asked to respond to the stimuli naturally, and the stimuli were delivered at random in each trial. Due to there being no prepared movement the startle elicited startle reflex instead of StartReact. Their results indicated that spastic stages of recovery had a heightened response to startle reflex than non-spastic stages. They consider the exaggerated responses in spastic stages as evidence of RetST hyper excitability; therefore, this led to the idea that RetST plays a key role in the development of spasticity. Conceivably, startle reflex can be used to determine excitability in the RetST after stroke (Li et al., 2014), but it is important to note that the impact of excitability of the RetST on functional recovery is not known (Li et al., 2014). StartReact and startle reflex are both options that present unique ways of studying the RetST after stroke.

2.3 Prepulse Inhibition and Prepulse Facilitation

PPI is an inhibition of the startle response by a non-startling stimulus (prepulse) which is administered before the startling acoustic stimulus (Braff et al., 2001; Maslovat et al., 2012; Nusbaum & Contreras, 2004). In contrast, PPF is an increase in the startle response by a non-startling stimulus (prepulse) which is administered before the startling acoustic stimulus (Plappert et al, 2004). In the current series of studies proposed for the completion of a doctoral degree, and where the ultimate aim

of the studies is to examine the effect of AMF in neurorehabilitation of stroke survivors, use of experimentation in StartReact context is the main methodological approach. Generally, a 'warning' (non-startling) stimulus, is followed by a 'go' stimulus that requires a participant to respond by executing a voluntary task (i.e., most trials are completed in a simple RT context). In random trials, the 'go' signal is paired with a startling stimulus and the motor response elicited can be compared with trials in which the startling stimulus was not present. Correct ISI between the 'warning' non-startling and 'go' with startling stimuli for PPI and PPF are needed in the stroke population to complete a StartReact protocol that utilizes a 'warning' signal. Currently, no previous study has examined PPI or PPF in the stroke population. PPI has been studied in many other neuropsychiatric disorders.

PPI was first used as a modification method to the startle reflex (Maslovat et al., 2012). PPI is now used as a measure of sensorimotor gating (Aasen et al., 2005; Braff et al., 2001; Nusbaum & Contreras, 2004). Sensorimotor gating is the filtering of environmental sensory information (Aasen et al., 2005; Braff et al., 2001; Nusbaum & Contreras, 2004). Sensorimotor gating is a method of suppression of motor responses to stimuli that are not significant (McAlonan, 2002). The stimuli that are not significant are "gated out" to allow the attention to be concentrated on the stimuli that are important (Braff et al., 2001). As seen in PPI, the prepulse is delivered a short period of time before the startling acoustic stimulus and the participant does not respond as intensely to the startling stimulus because it is still processing the prepulse (Aasen et al., 2005). An impairment in sensorimotor gating is seen in certain neuropsychiatric disorders that are known to be deficient in suppression of outside stimuli, such as Obsessive-Compulsive Disorder, Schizophrenia Spectrum Disorders, Tourette's syndrome, Huntington's disease, Autism Spectrum Disorders, Posttraumatic Stress Disorder, and Asperger's Syndrome (McAlonan, 2002; Miller et al., 2019).

In PPI, the time between the prepulse and the pulse, i.e., the ISI, is imperative in what response is produced (Fendt et al., 2001; Maslovat et al., 2012). For startle to be inhibited, the effective ISI is controversial in which researchers show different results of time for inhibition. In the literature, ISI that elicited inhibition were different when the subjects served in the study were healthy subjects (Ludewig et al., 2003). The consensus is the maximum time to elicit an inhibition between prepulse and pulse is 500 ms. The strongest inhibition of startle is thought to be produced when the time of prepulse is between 40-150 ms before the pulse (Fendt et al., 2001). Braff et al. (2001) believe the maximum inhibition is when the prepulse is around 120 ms before the pulse.

PPI can be increased in multiple ways. One method of enhancing PPI is with increased intensities of the prepulse (Braff et al., 2001; Fendt et al., 2001). However, increasing the intensity of the prepulse will only enhance PPI up to the point at which the startle threshold is recognized (Fendt et al., 2001). Another way of increasing PPI is using the same modality of prepulse and startling stimulus (Maslovat et al., 2012). Using the same modality for the stimulus and prepulse can increase the inhibitory effect of the prepulse, as current research has proposed different pathways are used for the different prepulse modalities (Maslovat et al., 2012). This is not to completely rule out the use of different modalities as some work has shown the effective inhibition by use of different modalities. Different modalities still produce PPI, so PPI does not strongly depend on modality (Fendt et al., 2001).

Less work has been done on PPF than PPI. PPF is thought to be an orienting or attentional mechanism (Hong et al., 2008). In rats and mice PPF has been shown when the ISI is between 0-10 ms (Plappert et al., 2004). In contrast, Aasen (2005) reported PPF is present when the ISI is 500-2000ms. After 2000 ms there is no effect seen from the prepulse. In the examination of effectiveness of AMF for neurorehabilitation using experimentation in StartReact context, determination of ISI that create PPF in stroke survivors are needed because this may create a bigger change in EMG or movement variability.

2.4 Impairment Levels

Determination of the level of motor impairment in stroke survivors prior to inclusion in the current series of studies is important for the inclusion/exclusion criteria because study 2 will exclude participants who cannot achieve a two or more on the Oxford scale at the wrist. It is also important for interpreting outcomes at the end of the study. This can give insight into how level of impairment correlates with StartReact response. Impairment levels after a stroke vary depending on size of the lesion, location of the lesion, and damage to the CST (Ciccarelli et al., 2008; Honeycutt & Perreault, 2014; Langhorne et al., 2011). Impairment after a stroke can emerge as a multitude of disabilities that are exhibited on their own or most often in conjunction with other disabilities. The impairment can be to the arms and legs, speaking, understanding, reading, and writing, swallowing, vision, bowel and bladder control, fatigue, memory, and skin sensations (Geyh et al., 2004). Motor impairment is however the most commonly recognized impairment (Langhorne et al., 2011).

Diffusion-based tractography can be used to map out a lesion in the brain. Studies using tractography to show fractional anisotropy have produced results that demonstrate as the integrity of the CST is decreased the functional outcomes are decreased. The functional outcomes were measured using neurological scores (Ciccarelli et al., 2008). Ciccarelli (2008) produced a review on diffusion-based tractography. The review described ways the brain reorganizes after neurological disorders. During stroke recovery the size of the lesion has a correlation with the functional remapping done by the brain, and impairment level. The same review also explained how tractography can be employed to monitor improvement knowing the location of the lesion in the brain. The location can give an explanation as to why the stroke has produced the symptoms that are shown in the individual. This is important from a clinical perspective because changes in the tractography over time are signs of progression and can

predict the outcome (Ciccarelli et al., 2008). In future, tractography has the means to aid in treatments and rehabilitative therapies for the individual patient (Ciccarelli et al., 2008).

Other ways of determining impairment levels after stroke are the use of quantitative measures, such as the Fugl-Meyer Assessment, and the Oxford Scale. The Fugl-Meyer Assessment is a quantitative impairment index that is used in most research involving stroke and was created specifically to measure recovery after stroke (Gladstone et al., 2002). The Fugl-Meyer Assessment is divided into 5 domains that can be used alone or divided into subsections. The domains are: motor, sensory, balance, joint range of motion, and joint pain. Reliability and validity tests have been done on the Fugl-Meyer Assessment and its subsections. Multiple studies results are in support of the use of the Fugl-Meyer Assessment. Of the 5 domains, the motor domain will be the one used in the first study of this thesis. The motor domain has an assessment of upper extremity and lower extremity that studies have established good reliability and validity of the scales as indicators of motor impairment (Gladstone et al., 2002). The Oxford scale or Medical Research Council (MRC) Scale is a method of determining muscle strength. It is widely used in a range of populations and different muscle groups. It uses a 0 – 5 grading scale with zero being no movement and five being normal movement. A study done by Gregson et al., (2000) found the MRC scale to be reliable in the elbow, wrist, and knee in a population of acute stroke participants. The Oxford Scale will be used in the second study of this thesis to measure the strength in the wrist. The inclusion criteria will only allow those who score at least a two.

Knowing the impairment levels of an individual who has had a stroke is important when StartReact is applied (Choudhury et al., 2019). The StartReact response that is seen in individuals will depend on their level of impairment. In the study done by Choudhury et al. (2019), 95 individuals who had suffered a stroke performed a wrist flexion movement under the StartReact protocol. Their results show a negative correlation between the StartReact response and their upper limb functional

measurement (Action Research Arm Test). The higher the impairment of an individual the greater the response to StartReact. The proposed explanation for this finding is that the highly impaired individuals have more damage done to the CST and therefore rely on a strong RetST. As stated before, StartReact is hypothesized to be a measurement of RetST activity hence why an individual with greater impairment would have an increased StartReact response.

2.5 Movement Variability

Bernstein famously wrote about variability in 1967 describing it as "repetition without repetition". Bernstein was a Russian physiologist and biomechanist that, through his own experimentation, laid down a foundation in motor control that has been built on ever since (Davids et al., 2003). The quote "Repetition without repetition" is explaining that if multiple repetitions of a movement are attempted, no two movements will be identical (Stergiou & Decker, 2011; Lockhart & Stergiou, 2013). Such variability in the completion of motor tasks stems from an abundance of working parts or elements which should be coordinated for the execution of the tasks (Harbourne & Stergiou, 2009). In the motor control literature, theorists have proposed differing views on movement variability. Early investigators saw variability as a source of noise or error in the completion of movements which should be reduced or eliminated. The interest in variability has increased due to the more recent view that variability is an important aspect of the movement which should be exploited, in contrast to what previous investigators believed. Contemporary definitions of movement variability explain it as the variations that are present when tasks are completed multiple times (Harbourne & Stergiou, 2009; Stergiou & Decker, 2011).

The presence of variability in movements allows for adaptive and flexible movements that are not reliant on changing contexts (Hamill et al., 1999). Common behaviors such as: control of orientation and/or postural control in the face of varying force fields, and successful completion of multiple

rhythmical processes (such as gait) demonstrate the importance of examination of movement variability (Hamill et al., 1999). Variability is now perceived as a sign of a healthy movement system (Harbourne & Stergiou, 2009), and new hypotheses, attempting to explain the way the human movement system works by analyzing variability, have been established. Three relevant theories commonly used in the literature include dynamical systems theory (DST), uncontrolled manifold hypothesis (UCM), and generalized motor program theory (GMPT).

A dynamic system is a complex, nonlinear system whose behavior changes over time (Bar-Haim et al., 2008; van Emmerik et al., 2016). In the literature, dynamical systems are often described with differential equations (Layek, 2015). The theory known as DST of movement was first described by Haken (1985). In Haken (1985) experiments, investigators noticed adaptive patterns in hand movements with changing movement parameters and paired this phenomenon with mathematical equations that were created for the study of nonlinear movements. DST is based on a multidisciplinary approach in understanding human motor behavior that includes mathematics, biology, psychology, physics, and chemistry (Davids et al., 2003; Jensen, 1990). In this theory the biological system exhibits self-organizing (stability-seeking) behavior, depending on internal (to the organism) and external constraints (e.g., movement instructions, requirements) and (environmental) contexts, and observed movement is the result of complex interactions between multiple subsystems internal and external to the body (Jensen, 1990; Stergiou & Decker, 2011).

As stated above, traditional views on human movement and movement variability are diverse (Stergiou et al., 2006). Importantly, movement variability was initially described as error and movements that are skilled were described as movements with a decreased variability (Harbourne & Stergiou, 2009). These views on variability as a consequence of noise in the movement were disregarded by the DST which views variability as essential in the dynamics of the movement and as a source of change in

behavior (Hamill et al., 1999). In DST, an optimal variability is associated with every movement, and any variation from the optimal variability (either increased or decreased variability) is undesirable. An increase in variability can indicate instability whilst decreased variability represents lack of flexibility. Therefore, a decrease in variability makes a behavior highly stable without the ability to adapt to the changing environment and requirements of the task (Harbourne & Stergiou, 2009; Stergiou & Decker, 2011).

DST literature often refers to the term '*nonlinear*,' where the organization of a biological system is described as *nonlinear*. *Nonlinearity* in a system means its input and output are disproportional with one another or 'not in a straight line'. *Nonlinearity* is represented by a sequence of *bifurcations*, when a new behavior output is produced due to an input that creates a change in the stability within the system (Camazine et al., 2001). A classic example of such *nonlinearity* in human movement is walk-to-run transition with increasing walking velocity.

Central to the DST movement is the concept of *self-organization*, which has been defined in multiple ways. In DST, *self-organization* is an emergent pattern from smaller components within the greater system that seek stability after perturbation (Camazine et al., 2001). A *nonlinear* system seeks new stability in the face of perturbation through *self-organization*. *Self-organization* can be identified by the presence of two *parameters: control* and *order parameters*. The *control parameter* is the parameter being manipulated that creates a change in the *order parameter*, which in turn captures the collective behavior of the system. The bifurcations that characterize a *nonlinear* system are the result of inconsistent changes to the *order parameters* due to constant changes in the *control parameter* (Stergiou, 2016). When compared with a linear system a *nonlinear* system has more complexity, which calls for the use of equations that will accommodate to *nonlinearity* (Harbourne & Stergiou, 2009). *Nonlinear* equations are used to measure the amount of variability in the system and provide

information about the temporal variations in the movement. The *nonlinear* measures and tools used in the study of *nonlinearity* in the human motor system, mainly originate from the *'chaos theory'* used to examine variations in phenomena which display deterministic patterns (Stergiou et al., 2006). As opposed to linear measures, that offer information in regard to the signal quantity and provide descriptions about the magnitude of variability around a central point, nonlinear measures provide information on the structure of variability (Harbourne & Stergiou, 2009; Stergiou & Decker, 2011).

DST emphasizes behavioral transitions at critical points when the variability has increased to a point where the stable system becomes unstable and a new, less variable, behavior emerges (Bar-Haim et al., 2008; Harbourne & Stergiou, 2009; Stergiou & Decker, 2011). To provoke the increase in variability, a perturbation is introduced to the system. An example of the critical point is explained in Harbourne and Stergiou (2009): A child learning to ride a bike. First, the child has training wheels on the bike and the behavior is stable. Then the training wheels are taken away and this perturbs the system. The behavior is unstable as the child attempts to control the bike without training wheels. This becomes the critical point at which the unstable behavior without the training wheels may shift to a stable behavior of controlling the bike. When the child can ride without training wheels, the behavior is stable, and shows low variability.

UCM literature has a view of movement variability associated with a specific definition of synergy. A synergy is formed when the system is organized in a way that stabilizes performance variables (e.g., by reducing endpoint variability; Vaz et al., 2019). As explained in Latash et al. (2010) a synergy can be broken down into a neuromotor hierarchy i.e., joint, limb, muscle, ion channels, etc., which contribute to the production of movement. At each level redundancy exists. Motor redundancy (later Latash coined the term motor abundancy to express the same opinion) is applicable when a task being given multiple motor solutions due to the redundant number of elements (degrees of freedom)

than are available to solve the task (Latash et al., 2010; Stergiou & Decker, 2011). Bernstein was the first to document motor redundancy as a problem with degrees of freedom: i.e., the problem of selecting specific motor elements to execute a task. UCM was first developed and published by Scholz and Schoner (1999) as a method for analyzing elemental variables trial to trial variability to determine if there is a stabilization effect on performance variables. UCM was then further used in Latash et al. (2002), to attempt to answer the problem of motor redundancy.

The 'uncontrolled manifold' within the UCM is the subspace within the state space formed by the range of possible values of elemental variables (degrees of freedom) in a task. According to Vaz et al. (2019), uncontrolled comes from the theory that within the redundant degrees of freedom a specific variability type does not need to be controlled. There are two main components to the variability of the elemental variables in the UCM. One is deemed as 'good' and influences achieving a performance variable (e.g., achieving a target in a goal-directed movement), and another is classed as 'bad' and does not contribute to achieving the performance variable. To measure and analyze synergy, uncontrolled manifold uses a synergy index which is defined as: (VUCM - VORT)/VTOT. Where VUCM is the performance variable variance associated with achieving the goal, VORT is the orthogonal component (performance variable variance not associated with achieving the goal), and VTOT is the total variance possible in the system. VUCM and VORT need to be normalized by multiplying by the Degrees of Freedom. Normalization allows for a comparison between the two components. In instances where VUCM is larger than VORT this is an indication that a synergy formed between elemental variables has a stabilizing effect on performance variable, and if VUCM is lower than VORT this indicates a destabilizing effect on the performance variable by the elemental variables (Latash et al., 2010; Vaz et al., 2019).

GMPT stems from Schmidt 1975, first introducing a generalized motor program in Schema Theory. Since then, motor programs have been extensively researched in multiple disciplines and the

world of motor learning has expanded through researching the subject intensively (Shea & Wulf, 2005). A generalized motor program is a template that provides a foundation for generating a movement sequence within a class (Kelso, 1997; Kwon et al., 2011; Lai & Shea, 1998). A class of movements use the same invariant features (Kwon et al., 2011). The invariant features in the class are sequence order, relative timing, and relative force (Lai et al., 2000). From this definition, GMPT is the idea that once a movement is established and stored as a memory, it becomes a plan. The plan can be used in multiple movements by adjusting its parameters (invariant features) according to the skill needed, or the goal (Kwon et al., 2011; Summers & Anson, 2009). GMPT suggests there is a hierarchical control of the movement. It is suggested to explain movements that occur in 200 ms or less, which are considered open loop (Schmidt, 1975).

In a RT context, Schmidt (1975) put forward the concept that outside perturbations cannot cause a new movement or adaptation in the ongoing one (e.g., blocking of a movement which is started), for roughly 200 ms, and until the current one has completed its reaction to the imperative stimulus. This concept of generalized motor programs, was however, dependent on movement experience and hence on Adam's closed loop theory (Adams, 1971). In the beginning stages of a system developing a schema, Schmidt (1975) stated that an increase in variability created an increase in schema strength. Furthermore, the schema or plan that was created would show a decrease in variability with repetition and experience enhancing the movements efficiency. Consequently, variability of the movement in GMPT is seen as noise or error in the system (Stergiou & Decker, 2011). Noise in the system in this traditional view is seen as a nuisance that must be minimized to increase proficiency of the movement (Button et al., 2003).

A key point all three theories agree on is decreased variability is the result of an efficient movement (Stergiou & Decker, 2011). This is important for future development of studies that are

investigating variability in human movement. However, variability is a normal occurrence in every movement. Not only has it been shown to be important in motor learning literature, it has been shown in studies of organ systems such as heart rhythm, and brain waves (Myers et al., 2009).

Recently a new theory, stemming from DST, has been presented in the literature. The theory is proposed in Stergiou et al. (2006) and states that within the biological system the variability has an 'optimal' amount of variability present. When a biological system has the optimal amount of variability it is stable and able to adapt to perturbations. The optimal amount of variability can be an indicator of health, and takes on a complex, chaotic form. The theory of optimal movement variability was developed based on the literature surrounding variability in other biological systems (Kaipust et al., 2013). According to Stergiou et al. (2006), any variability that is lower than optimal amounts will make the movement rigid and less adaptable. Any variability that is higher than optimal amounts will make the movement noisy and destabilized. Either change to variability, whether increased or decreased, is a sign of an unhealthy system. This is seen in variability analysis of gait in the elderly. When otherwise healthy elderly participants' gait was analyzed compared to healthy younger participants' gait, an increase in variability was seen. The increased variability in the elderly population resulted in the belief it is a reason of instability and higher risk of falling (Buzzi et al., 2003; Kaipust et al., 2013; Myers et al., 2009). In individuals who have a compromised movement system, variability is not in the optimal range. This change in variability, whether increased or decreased, will make adapting to movements difficult.

Stergiou (2006) indicates the use of nonlinear tools could be used to detect variability in motor behavior. Using nonlinear tools in measuring variability in a healthy system can help in the search to understand variability in the compromised movement system (Buzzi et al., 2003). For example, in studies done on pathological gait, gait has been shown to be either too periodic and predictable, or

disordered and random, in comparison to a healthy gait during locomotion that shows natural stride-to-stride fluctuations (Kaipust et al., 2013; Myers et al., 2009).

In the literature, studies that are measuring variability are looking at two possible types of variability. One is endpoint variability, which is associated to the goal, and the other is coordinative variability which is associated to performance (van Emmerik et al., 2016). In Schwarz et al. (2019), authors sought to develop an accurate assessment of upper limb impairment after stroke using measurements of coordinative variability. Having an accurate measure is imperative in evaluation, and monitoring impairment. Authors associated impairment after stroke with a reduced amount of movement variability. In this study four chronic stroke survivors underwent 30 daily living tasks. These tasks were selected to utilize the whole upper extremity. In three of their four participants the impaired limb showed a lower variability than the non-impaired limb. Only one subject showed an increased variability in the impaired limb, and this was believed to be due to compensatory movements. Authors believed this was preliminary evidence that stroke survivors' level of impairment can be measured based on the amount of movement variability using their equations. Limitations to this study include their sample size. A larger sample size is needed to clarify if the results are accurate across a wider group of stroke survivors. Also, a control group of non-impaired individuals would benefit this study to compare the results of the impaired arm in the experimental group to the control group.

In Ranganathan et al. (2019), their hypothesis was that in stroke survivors the impaired limb would show higher variability than the nonimpaired limb, and the variability would be modified depending on the task. In this paper, the variability being examined was an example of endpoint variability. The authors used eleven stroke survivors and eleven age matched healthy controls. The task was a goal driven task that required the participant to move one or both arms to get a cursor to a target. The results showed that in both groups variability in each arm was modified depending on the task at hand. This is consistent with previous literature results that variability seen in stroke survivors is not

completely noise, and there is some active control. In the unimanual tasks the impaired limb showed an increased amount of variability than the non-impaired limb and showed an increased amount of variability when compared to the control group. When comparing the Schwarz et al. (2019) study to the Ranganthan et al. (2019) study the amount of variability seen within the stroke survivors is different, and this can be attributed to the fact that they are measuring two different types of variability. A major limitation of Ranganthan et al. (2019) was diversity of functional abilities within the cohort.

Hammerbeck et al. (2017) is another study that utilizes endpoint variability. Authors wanted to learn if improvements in reaching are possible after four days of training at multiple training speeds. The protocol was a simple targeted reaching task. The endpoint location of each trial was documented, and the results showed an improvement of endpoint accuracy by a reduction in endpoint variability after the training. The study also limited trunk movement which has been shown in previous studies to help improve movement quality by reducing compensatory movements. This is an advantage to their results by showing the endpoint accuracy was not affected by trunk movement. Hammerbeck et al. (2017), study was a pilot study and for long term effects to be seen in stroke survivors the training potentially needs to be longer. This study shows evidence, in chronic stroke survivors, there is the possibility of learning to control variability. It also shows that in chronic stroke survivors whose movements are rigid and stable, there is a possibility for improving performance of existing movements.

Sethi et al. (2013) is another paper that looked to analyze the upper extremity movement variability in stroke survivors. Authors tested the impaired upper limb of individuals who have had a stroke and compared it with the non-dominant upper limb of healthy controls. Participants were asked to reach and grasp a soda can. Movement kinematic was examined by tracing markers on the shoulder, elbow, wrist, and proximal interphalangeal joints. What sets this study apart from other studies is the analysis. One measurement was standard deviation (SD) of the shoulder, elbow, wrist, and proximal interphalangeal angles, and another measure was the temporal structure of variability (Approximate

entropy: ApEn) of shoulder, elbow, wrist, and proximal interphalangeal angles. These represent linear (SD) and nonlinear (ApEn) measures. The use of nonlinear measurements in stroke survivor's upper extremity is minimal in the literature. In Sethi et al. (2013) results the SD measures showed a higher variability than healthy controls. The ApEn measure of variability showed statistical significance and was a decreased amount of variability in stroke survivors. Authors used the ApEn results to demonstrate that it is aligned with the optimal variability theory. Healthy controls demonstrated chaotic temporal variations that are adaptable to perturbations. The stroke survivors showed a decrease in ApEn which demonstrates a decrease in variability, therefore their movements were more rigid and less adaptable.

More studies are needed that look at nonlinear measurements of parameters related to the upper extremity in stroke survivors. This is needed to create a greater understanding of post stroke movement variability. The nonlinear measure results in this study show that there is a possibility of taking advantage of the DST concepts in designing new interventions for stroke rehabilitation. In such an approach, post-stroke motor impairments will be characterized by a stable dynamic (with decreased variability of the segmental/joint synergies involved) which can be perturbed to increase the variability of the synergies formed. At a critical point, new functional abilities (leading to improved endpoint accuracy) may emerge, and the movement will become more stable. The results also show how a linear measure, and a nonlinear measure can give differing results. This is an important fact to understand when deciding which measures to use in an evolving study. The linear measurement of SD in this study did not show a difference in healthy movement compared to controls, when in fact there was a difference in other measures of variability. The use of nonlinear measures could create a larger understanding of impairment and how to create more rehabilitation measures that improve function.

The importance of variability in all biological systems is shown in the literature. It has been studied in multiple disciplines and proves to need a deeper understanding. Variability in the motor control literature learns from other biological systems. Movement variability has produced multiple

theories over time since Bernstein's breakthrough study in 1967. Theories such as DST, UCM, and motor program theory are prominent in the literature. The theories also give a different debate of nonlinear measures versus linear measures. It is important in stroke research to utilize the theories in movement variability to increase understanding in movement post stroke. The theory of optimal variability shows promise in further investigation, particularly in a clinical setting. Using this theory, it would be possible to measure and analyze the amount of variability in movements from individuals who have had a stroke. Movements are often described as rigid and stable despite increased endpoint variability in goal-directed movements. This is in line with the idea that this is a sign of decreased variability at the joint/segment level creating a rigid movement. Further investigations are needed to use the theory of optimal variability and attempt to increase the variability of stable movements. Stroke is the leading cause of adult impairment and continues to rise with time. Better rehabilitation techniques are needed to help stroke survivors' functional capabilities and therefore quality of life.

2.6 Conclusion

The aim of this literature review is to provide current evidence for the suitability of AMF (i.e., RetST) as a means for rehabilitation after stroke. The neural pathways that make up the AMF originate in the brainstem, and project to areas of the spinal cord along similar projections as the CST. RetST activity is triggered during the StartReact context. There are human and animal evidence that StartReact might be usable to help in the rehabilitation process after CST damage. Both human and animal studies indicate that the RetST innervates the upper limbs throughout the arm, including the hand. AMF may be less impaired after a stroke; making it a potential pathway to use in rehabilitation. To determine if AMF are a feasible method for use in rehabilitation, this proposal seeks to identify greater movement variability in involuntary movements than in voluntary movements. Movements after a stroke have been found to be less variable, so an increase in variability could lead to improved overall function. The

following series of studies was outlined to examine the effectiveness of AMF for the rehabilitation of stroke survivors.

- Study 1: A Systematic Review of the Effects of StartReact on Motor Responses in Stroke and Healthy Individuals.
- Study 2: Determination of Prepulse Inhibition and Prepulse Facilitation in Stroke Survivors.
- Study 3: StartReact Influences Upper Limb Kinematic and Endpoint Accuracy in Reaching.

Chapter III A Systematic Review of the Effects of StartReact on Motor Responses in Stroke and Healthy Individuals

3.1 Abstract

Published in Journal of Neurophysiology see Appendix G.

Introduction: Control of limb movements may be impaired after stroke due to the loss of connectivity between the cerebral cortex and spinal cord. A notion to improve motor function in stroke survivors is to employ AMF, such as the RetST, which originates from the brainstem and terminates at different levels of spinal cord. One way of targeting the RetST is to use a "StartReact" protocol to foster premature release of a pre-planned movement in response to a startling stimulus. Our aim was to find support for the preservation of such StartReact effect in stroke survivors.

Methods: We conducted a systematic review with meta-analysis of literature published in English up to September 2020, to explore differences in motor responses to startling stimuli in StartReact effects. The protocol of the study was registered (PROSPERO Registration No: CRD42020191581). PubMed, Google Scholar, Web of Science, PsycINFO, and Science Direct were searched for relevant literature. The meta-analysis contained six studies involving a total of 151 stroke and healthy participants. Muscle onset latency data was extracted from the qualifying studies and compared using RevMan.

Results and Conclusions: StartReact effect was present in both stroke and healthy groups, represented by shortened muscle onset latency when startling stimulus was present. There was considerable heterogeneity of the outcome measures, which was attributed to the range of motor impairments among stroke survivors and methodologies employed. Our findings support the notion of preservation of preprogramming ability and suitability of RetST and StartReact effect for motor rehabilitation following stroke.

3.2 Introduction

The previous chapter provides evidence of published studies investigating the RetST in animals and humans. This evidence provides a basic understanding of the role of the RetST in the motor control system and where there is potential for it to be used. The previous chapter also demonstrates methods in the literature that are used to stimulate the RetST. A promising method being the StartReact paradigm. The literature on StartReact is in the non-clinical population and various clinical populations. While no two clinical populations will respond in the same way it is necessary to understand directly how the stroke population responds in such a concept.

The following systematic review and meta-analysis was conducted to provide background information on the StartReact paradigm and to provide guidance on the current literature involving the stroke population in StartReact. It will also elucidate existing methodologies used in the StartReact literature and how the methodology is separated from other theories such as startle reflex and stimulus intensity effect.

Stroke is a leading cause of movement disability (Stroke Association, 2018). In the UK alone, there are 1.2 million stroke survivors, two-thirds of whom live with a disability secondary to stroke (Stroke Association, 2018). The type and severity of motor disability caused by stroke is varied, and there is an urgent need to develop new rehabilitation methods to help improve motor disability in stroke survivors. Many neurophysiological characteristics have been investigated to identify and employ features that might be exploited to improve stroke rehabilitation outcomes. One such characteristic is the startle response (Maslovat et al., 2012) and StartReact effect. Investigations looking into the StartReact effect have peaked interests across multiple clinical populations such as hereditary spastic paraplegia (Nonnekes et al., 2014), Stroke (Carlsen et al., 2012; Choudhury et al., 2019; Coppens et al., 2018; Honeycutt & Perreault, 2012; Honeycutt et al., 2015; McCombe-Waller et al., 2016; Rahimi &

Honeycutt, 2020; Yang et al., 2019), and Parkinson's (Nonnekes et al.,2015). These populations exhibit faster RT in StartReact effects despite the apparent motor impairment which could be attributed to motor programming and/or the execution of the movement (Carlsen et al., 2012; Honeycutt & Perreault, 2012; Rahimi & Honeycutt, 2020).

In a simple RT experimental context, the premature release of a preprogrammed motor response elicited by a startling (mostly loud auditory) stimulus, delivered simultaneously with the imperative 'go' signal, is called the StartReact effect (Maslovat et al., 2012). It has been suggested that the startling stimulus excites the subcortical structures, and the prepared action is released with a shorter latency when compared to movements without startle. In contrast to classical RT literature, StartReact literature uses EMG onset latency of the agonist muscle (PMT) as a measure of RT (Carlsen et al., 2012), and the presence of StartReact effect can therefore help elucidate whether the participant has maintained motor programming ability (Carlsen et al., 2012; Honeycutt & Perreault, 2012). Several studies specifically refer to the involvement of the RetST in the shortening of the PMT and associated RT in producing StartReact effect (Baker & Perez, 2017; Carlsen et al., 2012; Carlsen & Maslovat, 2019; Choudhury et al., 2019; Honeycutt & Perreault, 2012). This is important to stroke survivors with residual motor impairments because the RetST is sometimes spared, and as indicated above, might be a target of rehabilitation aimed at improving motor function (Honeycutt et al., 2015). Specifically, the presence of StartReact effect in stroke survivors can be a biomarker for the preservation of motor programming ability and involvement of RetST in movement execution, which in turn could serve as a possible alternate motor pathway for neurorehabilitation (Honeycutt & Perreault, 2012).

The presence of startle responses is determined by EMG in the SCM and/or OOC muscles (Carlsen et al., 2012,2007; Leow et al., 2018; Maslovat et al., 2012; Smith et al., 2019). In early studies on startle response, the OOC was the preferred measurement of startle, but recently, investigators have

been questioning the certainty of this way of measuring startle and the SCM is seen by some investigators to be a better option for measuring the startle response. This is due to the shorter RT in trials where there is a SCM startle response than when there is no response shown by the SCM (Carlsen et al., 2007; Leow et al., 2018; Smith et al., 2019). Moreover, in startle trials where a loud stimulus is repeatedly produced and there is a habituation affect, SCM is thought to be one of the last to become habituated making it, potentially, more suitable to measure a startle (Carlsen et al., 2007).

There are several small studies on StartReact in stroke, but there has been no report on the estimation of Effect Size for the observed outcome measures. The purpose of this systematic review was to review published literature on StartReact, and then use a meta-analysis of the qualified studies to assess the strength of evidence for StartReact effect in stroke survivors and healthy individuals. This systematic review included results of the studies that used EMG onset latency of the main agonist muscle for the execution of the motor task to determine presence of the StartReact effect. Moreover, as both the SCM and OOC have been used to determine a startle response, the present systematic review included studies that used either measure.

3.3 Methods

The protocol containing the outline of methods used (such as search strategy, data analysis, and data collection) was documented in PROSPERO Register of Systematic Reviews (Registration No: CRD42020191581). A systematic review of databases (PubMed, ScienceDirect, PsycINFO, Web of Science, and Google Scholar) was completed using key terms discussed and agreed upon by two reviewers. Searches were conducted using three keywords: RT, startle reflex, and StartReact. The development of the keywords followed PICO (Population, Intervention, Comparison, and Outcome) (Higgins et al., 2021) guidelines (Table 1). The database search was started in September 2020 and a final inclusion list was determined in November 2020.

Table 1

PICO table used in the database search

PICO	Definition
Population	Adult (≥18 years of age) chronic stroke survivors (>6 months post stroke) and healthy controls
Intervention	StartReact
Comparison	Stroke vs. Healthy
Outcome	EMG onset latency

All included studies were required to have an experimental group (sample of participants who have had a stroke) and a control group (no known diagnosis or healthy sample of participants). Inclusion criteria for the experimental group were adult participants (≥18 years of age), and chronic phase post-stroke (≥6 months) populations. The only brain lesion characteristics that were excluded were those with brainstem involvement. All types of motor impairment were included in the search. Control non-clinical individuals were neurologically healthy and reported no impairment. No restriction was put on the date and type of publication. Publications in English language were searched. Measurements (outcome parameters) inclusion criteria consisted of measurement of startle via surface electromyography (sEMG) of the SCM or the OOC, and/or PMT (RT) measurements determined by sEMG of the main muscle of the limbs used in the motor response. Meta-analysis was performed using the RT measurements to assess the strength of evidence for StartReact effect. We were aware of the difference between the definitions of premotor and RT in classical RT literature but noted that the two terms were used interchangeably in StartReact effects in the included papers.

Databases were searched for studies that met inclusion criteria. Using *RefWorks* (2018) and *Excel* a master list of eligible studies was created, and duplicates were removed. Titles and abstracts of the eligible studies were screened by two reviewers independently for inclusion in the review. The

outcome of screening was compared, and at this point it was mutually agreed that only studies that contained an experimental group (stroke) and a control group (healthy) would be reviewed. The independent review process was repeated and studies which were included by both reviewers underwent full-text assessment. Full-text assessment consisted of comparing included studies for the inclusion criteria, similarity of procedures employed, and appropriateness of the reported outcome measures. The reference lists of the remaining studies were checked for other eligible studies that were not found in database searches. After full-text assessment was completed by each reviewer, a list of qualified studies for review was created and the studies that were not agreed on were referred to a third reviewer to make the final decision. Table 2 documents the title and authors of each qualified study.

Table 2

List of qualified studies for review and meta-analysis

Title	Authors
The Relationship Between Enhanced Reticulospinal Outflow and Upper Limb Function in Chronic Stroke Patients	Choudhury, S., Shobhana, A., Singh, R., Sen, D., Anand, S.S., Shubham, S., Baker, M.R., Kumar, H., & Baker, S.N.
A startling acoustic stimulus facilitates voluntary lower extremity movements and APR in people with chronic stroke	Coppens, M.J.M., Roelofs, J.M.B., Donkers, N.A.J., Nonnekes, J., Geurts, A.C.H., & Weerdesteyn, V.
Planning of ballistic movement following stroke: insights from the startle reflex	Honeycutt, C.F., & Perreault, E.J.
Startling acoustic stimuli can evoke fast hand extension movements in stroke survivors	Honeycutt, C.F., Tresch, U.A., & Perreault, E.J.
Impaired motor preparation and execution during standing reach in people with chronic stroke	McCombe Waller, S., Yang, C.L., Magder, L., Yungher, D., Gray, V., & Rogers, M.W.
Impaired posture, movement preparation, and execution during both paretic and nonparetic reaching following stroke	Yang, C.L., Creath, R.A., Magder, L., Rogers, M.W., & McCombe Waller, S.

Note. Titles and authors of included studies.

Mean and SD of the EMG onset latency for the experimental and control groups were derived for each qualified study either by extracting them from the published papers, or where the study had not reported the relevant data, the corresponding author of the paper was approached via email and required data was requested. The data was analyzed within RevMan 5 software (2020). In 5 studies, the measurements of EMG onset time came from the upper limb. One study (Coppens et al., 2018), which had used measurements from a lower limb muscle, was retained because the current research was looking into the presence of StartReact effect in the stroke and healthy groups, regardless of the limb employed. We used a random-effects model to analyze differences of the EMG onset latencies in trials with and without the startling stimulus. Mean difference with a 95% confidence interval (CI) was

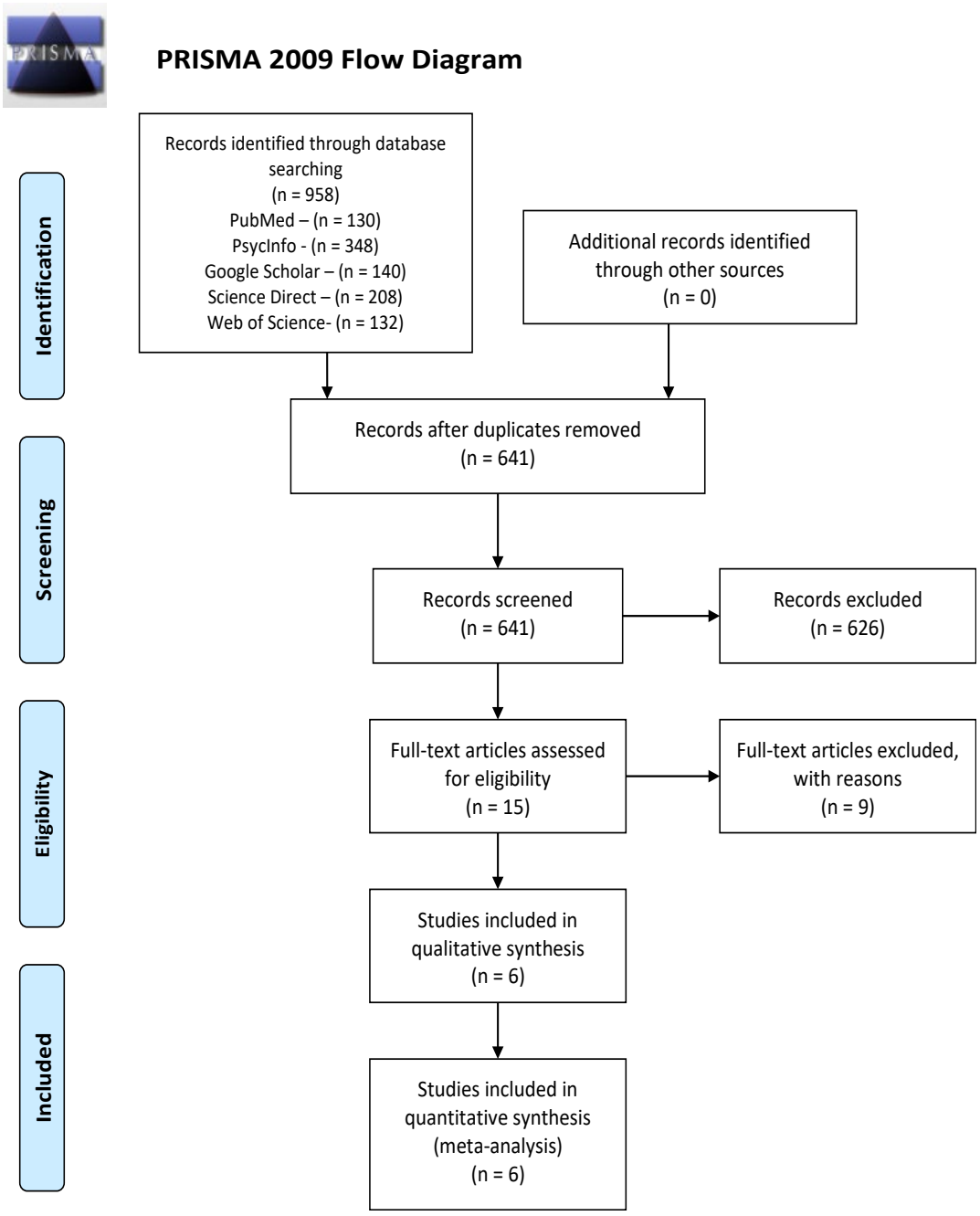
reported after pooling results of the qualified studies together. We calculated heterogeneity as the I^2 measure of consistency for each meta-analytic calculation. Risk of bias (RoB) in the qualified studies was assessed using the NIH quality assessment tool for before-after (Pre-Post) study without control group (National Heart Lung and Blood Institute, 2021). The tool assessed the RoB using 12 questions where each question could be given a Yes, No, or N/A (not applicable) answer, and a rating of Good, Fair or Poor.

3.4 Results

In the preliminary search of databases, 958 titles were available for selection before duplicates were removed. PubMed found 130 eligible studies, PsycInfo found 348 eligible studies, Google Scholar found 140 studies, Science Direct found 208 eligible studies, and Web of Science found 132 eligible studies. Duplicates were then removed leaving 641 possible studies. Of these, 626 studies were excluded after screening their titles and abstracts due to not meeting the inclusion criteria. Fifteen studies were full text assessed, and reference lists checked for other eligible studies. After full-text assessment, nine articles were excluded leaving six studies to be included in the qualitative synthesis and meta-analysis. Figure 1 is a flow diagram outlining the study selection process.

Figure 1

Prisma 2009 Flow Diagram



Note. PRISMA 2009 Flow Diagram (Moher et al., 2009) illustrating study selection process. Of the nine articles excluded, seven were due to study design, one was due to methodology, and one was due to RT measures not meeting inclusion criteria.

An overview of the characteristics of each qualified study is given in Table 3. The reported population inclusion criteria listed in the table of characteristics are the inclusion criteria for the stroke groups. Only two studies (McCombe Waller et al., 2016; Yang et al., 2019) provided a list of inclusion criteria for the healthy group, therefore the healthy inclusion criteria were left out of Table 3. The criteria for these two studies can be found in the notes of the table. 'warning' cues (auditory or visual) were used to instruct the participant to prepare to move and 'go' cues (auditory or visual) were the imperative signal to execute the movement.

Table 3

Characteristics of included studies

First author, year published	**Population inclusion criteria**	***Population Number***	***Motor Task(s)***	***Muscles with EMG measures***	***LAS timing***
Choudhury, 2019	Hemorrhagic or Ischemic Stroke Between 6 months-12 years post stroke No brainstem involvement No visual or auditory impairment Had not received botulinum toxin therapy in the preceding 3 months Scored 18 or above on a mini mental state examination	*Stroke n = 46* *Healthy n = 19*	*Isometric wrist flexion.* *Stroke group tested affected side* *Healthy group did not report side tested*	***Forearm flexor*** *(specific muscle not reported)*	*LED visual 'go' stimulus was randomly paired with a quiet (80 dB) or loud (110 dB) sound*
Coppens, 2018	>6 months post stroke Contralateral hemiparesis Capable to stand barefoot Normal hearing, normal or corrected to normal vision No medication that influences balance No impairment unrelated to hemiparesis Scored 24 or more on mini mental state exam	*Stroke n = 12* *Healthy n = 12*	*1) ballistic ankle dorsiflexion* *2) response to external balance perturbations* *Stroke group both sides tested* *Healthy group both sides tested*	***Tibialis Anterior,*** *Rectus Femoris*	*LED 'warning' signal followed by a variable time interval before the LED 'go' signal. The LAS (120 dB) was paired randomly with the 'go' signal in 25% of trials.*
Honeycutt, 2012	Unilateral brain lesion from stroke ≥ 1 year post stroke No aphasia	*Stroke n = 10* *Healthy n = 10*	*Elbow flexion and extension in dominant arm* *Stroke group tested affected side*	***Brachioradialis,*** *Triceps Long Head*	*2 auditory signals (80 dB). The first signal was the 'warning' cue, and the second signal was the 'go' cue. The LAS (128 dB)*

	Affected side was the dominant arm before stroke				*replaced the 'go' cue randomly.*
Honeycutt, 2015	No auditory impairment Chronic phase of stroke ≥ 1 year post stroke	*Stroke n = 8* *Healthy n = 10*	*Hand extension of the dominant hand* *Stroke group tested the affected side*	***Extensor Digitorum Communis***	*2 auditory signals of 80 dB. The first signal is the 'warning' cue, the second signal is the 'go' cue. The LAS of 128 dB replaced the 'go' cue randomly.*
McCombe Waller, 2016	>6 months post stroke Ability to stand unassisted Ability to follow commands	*Stroke n = 10* *Healthy n = 5*	*Standing reach by the affected side*	***Anterior Deltoid,*** *Middle Deltoid, Biceps Brachii, bilateral Tibialis Anterior, Soleus*	*LED visual stimulus used as a 'warning' and 'go' signal. In random trials the LAS (123 dB) was applied at time points: -1500, -1000, -500, -200, or **0 ms** with respect to 'go'.*
Yang, 2019	Unilateral cortical or white matter subcortical stroke 40 years and older ≥6 months post ischemic stroke or ≥12 months post hemorrhagic stroke Completed therapy Arm hemiparesis Ability to perform reaching movement	*Stroke n = 10* *Healthy n = 10*	*Standing reach to both sides*	***Anterior Deltoid,*** *Tibialis Anterior, Soleus, and Erector Spinae. Both sides tested.*	*LED visual stimulus used as 'warning' and 'go' signal. Randomly, the 'go' signal was paired with a LAS (123 dB) at -500, -200, **0 ms** with respect to 'go'.*

Note. If the study contained multiple times a LAS was delivered, the timing in **bold** was used. Data from muscles in **bold** were used for meta-analysis. Two studies (McCombe Waller et al., 2016; Yang et al., 2019) listed the following criteria as their healthy group inclusion criteria: neurologically healthy, no

musculoskeletal disorders affecting lower limbs, and cognitive ability to follow commands. In one study (Yang et al., 2019) one healthy participant was excluded from analysis, and healthy group was age matched with stroke group.

The RoB in each paper was determined by the same two reviewers who determined the inclusion list based on the results of the RoB assessment (Table 4). No study reported statistical power. Furthermore, only one study (Honeycutt et al., 2015) blinded the author in data analysis. However, In the current review reviewers agreed blinding was unnecessary, and a lack of blinding did not affect the amount of bias seen in the study. Studies clearly stated the question, inclusion criteria, outcome measures, and statistical analyses. The population used in each study was clearly stated. In three of the reviewed studies (Coppens et al., 2018; McCombe Waller et al., 2016; Yang et al., 2019), the stroke population was expected to be able to stand on their own. Reviewers felt this was not representative of a wider population of stroke survivors. The intervention to be used and consistency of delivering the intervention was accomplished in all studies except one (Honeycutt et al., 2015). In this study the intervention was delivered differently in the stroke and healthy groups due to impairment in the stroke group. Reviewers determined all studies had Good-Fair ratings.

Table 4

Assessment of Risk of Bias – NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

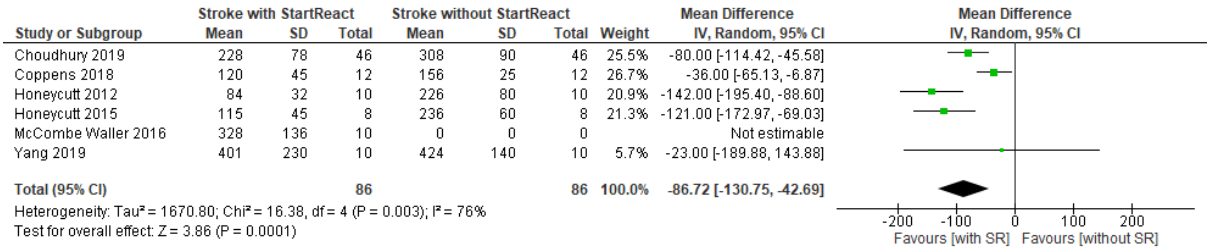
	Criteria											
	1	2	3	4	5	6	7	8	9	10	11	12
Choudhury, 2019 (G)	Y	Y	Y	Y	N	Y	Y	N	N/A	Y	Y	N/A
Coppens, 2018 (F)	Y	Y	N	Y	N	Y	Y	N	N/A	Y	Y	N/A
Honeycutt, 2012 (G)	Y	Y	Y	Y	N/A	Y	Y	N	N/A	Y	Y	N/A
Honeycutt, 2015 (F)	Y	Y	Y	Y	N	N	Y	Y	N/A	Y	Y	N/A
McCombe Waller, 2016 (F)	Y	Y	N	Y	N	Y	Y	N	N/A	Y	Y	N/A
Yang, 2019 (F)	Y	Y	N	Y	N/A	Y	Y	N	N/A	Y	Y	N/A

Note. Each question is given a yes (Y), no (N), or not applicable (N/A) score. G = Good; F = Fair. See Appendix A for full outline of questions in RoB assessment tool.

To estimate the effect of StartReact on stroke and healthy individuals, we pooled the available data and presented the results of the meta-analysis separately for stroke survivors (Figure 2) and healthy individuals (Figure 3). The mean difference in RT between trials with and without startling stimulus in the stroke group was -86.72 ms (95% CI: -130.75, -42.69). This was representative of a decrease in RT when StartReact was present. A considerable level of heterogeneity (I^2 = 76%) was present in the stroke group showing variability in the reported outcome measure. In Figure 2, RT data for trials without starting stimulus for one paper (McCombe Waller et al., 2016) was missing and reported as zero: the relevant data was not reported in the published article, and we did not receive any response from the authors after requesting it.

Figure 2

Outcome of the meta-analysis for stroke survivors

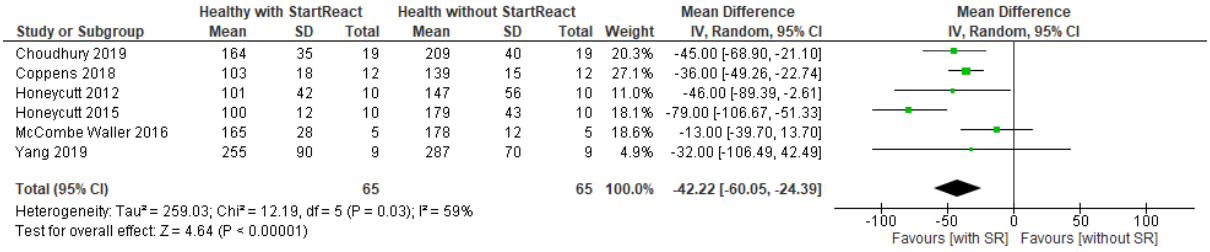


Note. Outcome of meta-analysis on the mean and SD of RT (EMG onset latency of the main agonist muscle) for stroke survivors. Data collected via email (Choudhury et al. 2019, Yang et al. 2019). No response received to our request for further data (McCombe Waller et al. 2016).

In the healthy group, the mean difference in RT between conditions with and without startling stimulus was -42.22 ms (95%CI: -60.05, -24.39). This was representative of a decrease in RT due to StartReact effect. A substantial level of heterogeneity (I^2 = 59%) was seen in the healthy group showing inconsistency in the reported outcome measures.

Figure 3

Outcome of the meta-analysis for non-clinical group



Note. Outcome of meta-analysis on the mean and SD of RT (EMG onset latency of the main agonist muscle) for healthy individuals. Missing data collected via email (Choudhury et al. 2019, Yang et al. 2019).

3.5 Discussion

In a systematic review of StartReact effect in stroke survivors and healthy individuals, a meta-analysis was used to assess the effect on motor responses (RT) of the startling stimuli. This is the first study to systematically search the literature for the StartReact effect in stroke survivors. For both groups, RT decreased when a LAS was present compared to trials with no loud stimuli (Figures 2 and 3).

The stroke group showed a much larger mean RT difference (more than double), between trials with and without startling stimulus, compared to the healthy group (-86.72 ms vs. -42.22 ms). As a result of the larger mean RT difference, we accordingly support the conclusion made by previous studies that the shortened onset latency of muscles was not only due to the involvement of subcortical area (RetST) in motor responses in StartReact effects (Baker & Perez, 2017; Carlsen et al., 2012; Coppens et al., 2018; Honeycutt & Perreault, 2012), but also the notion that the larger reduction in RT in stroke survivors was due to compromised CST (Choudhury et al., 2019).

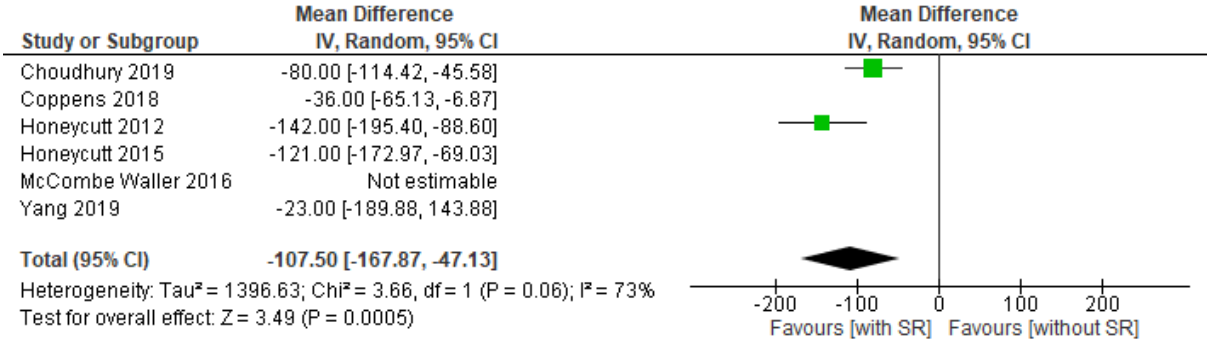
Results of the meta-analysis for the healthy group showed "substantial" heterogeneity (I^2 = 59%). Results of the stroke group showed "considerable" (I^2 = 76%) heterogeneity (Higgins et al., 2021). To further investigate source of heterogeneity, we sub-grouped studies based on our assessment of the RoB to determine the impact of differences in the quality of study design on the outcome measures (Figure 4). Two subgroups were created: one group with two studies (Honeycutt & Perreault, 2012; Choudhury et al., 2019) which had a rating of '*Good*', and the other group with 4 studies (Coppens et al., 2018; Honeycutt et al., 2015; McCombe Waller et al., 2016; Yang et al., 2019) with a rating of '*Fair*'. Results for the meta-analysis of the studies with '*Good*' quality (Figure 4 a-b) were mixed: considerable heterogeneity was present for the stroke group (I^2 = 73%), and the CI was wider -107.50 ms (95%CI: -167.87, -47.13), but no heterogeneity (I^2 = 0%), and narrower CI was found for the healthy group -45.23 ms (95%CI: -66.17, -24.30).

In contrast, results for the studies with '*Fair*' quality were consistent and similar to when all qualified studies were included in the meta-analysis (Figure 4 c-d): considerable heterogeneity was present for both stroke [I^2 = 75%; -68.22 ms (95%CI: -138.32, 1.89)] and healthy [I^2 = 75%; -40.95 ms (95%CI: -68.63, -13.27)] groups.

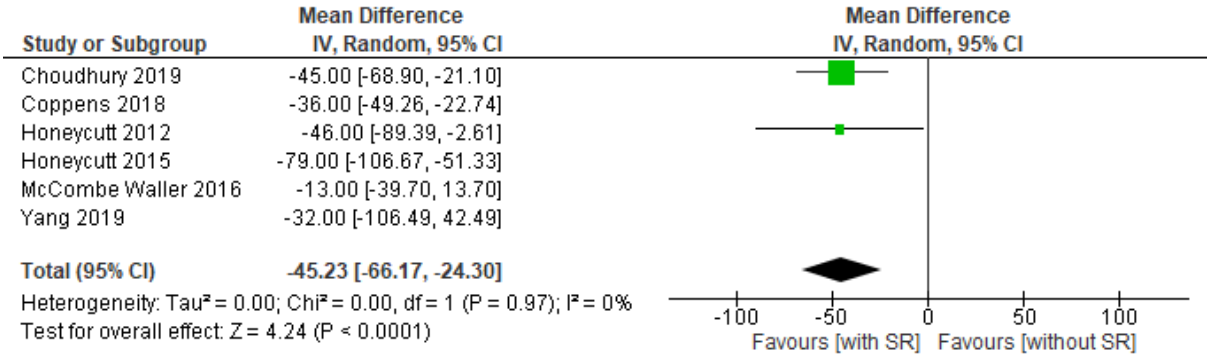
Figure 4

Outcome of meta-analysis on the RoB subgroup

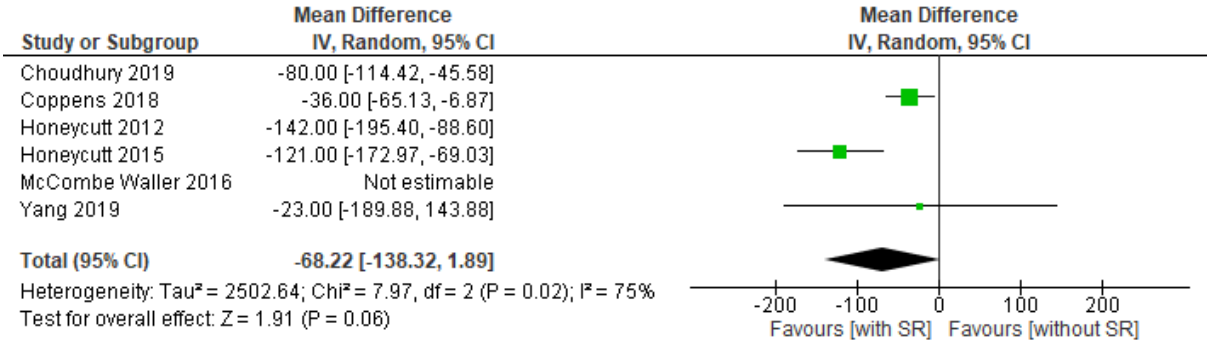
a

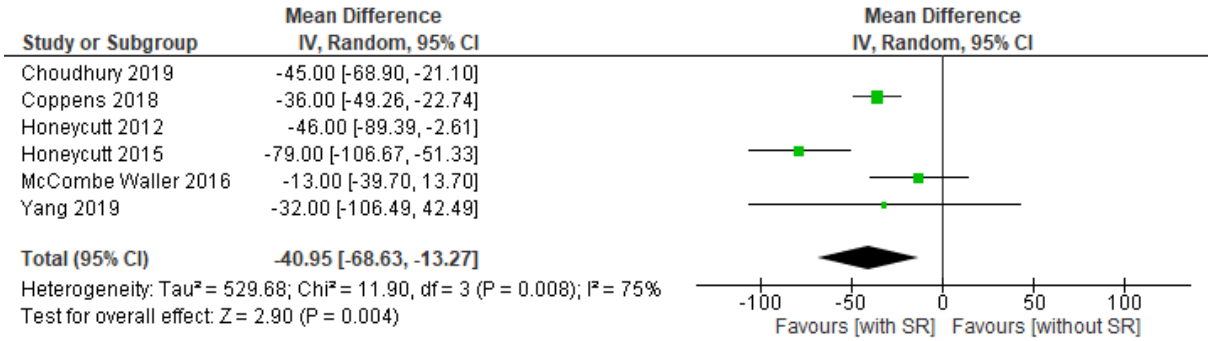


b



c





d

Note. Outcome of meta-analysis on the subgroup of studies. **(a)** Stroke group with a rating of Good, **(b)** Healthy group with a rating of Good, **(c)** Stroke group with a rating of Fair, **(d)** Healthy group with a rating of Fair.

The high level of heterogeneity and wider CI in the reported outcome measures for the stroke group could be due to the differences amongst study population and methodologies used in each study. Age, level of impairment and location of the stroke varied in each study, as well as the muscles measured for reaction time (Table 3). Studies were also different with respect to the intensity of the auditory stimulus employed and whether a visual stimulus was present. Only two studies (McCombe Waller et al. 2016, Yang et al. 2019) reported how they measured the acoustic stimulus intensity in their methods. Carlsen et al. (2007) showed premotor reaction time (PMT) decreased with increasing stimulus intensity, but in trials when SCM activity was present (an indicator of startle response), a significant reduction in PMT irrespective of the stimulus intensity was observed. During the review process for publication of the present study, we were accordingly recommended to pool together trials with or without a measure of SCM muscle activity and conduct a power analysis (below).

In the six qualified studies, there can be a subgroup created based on the presence of SCM muscle activity as an indicator of startle. Analyzes were repeated based on two groups: one group comprised of studies in which RT in trials with the loud auditory stimulus and SCM muscle activity was compared against trials without the loud auditory stimulus and SCM muscle activity. The second group

comprised of studies in which RT was compared across the two conditions in the absence of SCM muscle activity. Honeycutt & Perreault (2012), Honeycutt et al., (2015), and Coppens et al. (2018) formed the group with a measure of SCM. Choudhury et al. (2019) Yang et al. (2019) and McCombe-Waller et al. (2016) formed the latter group with no SCM measure.

The first group reported shorter reaction times in both stroke and healthy groups compared to the second group. This supports the notion that in future studies involving StartReact protocols, a similar check to confirm the presence of startle in response to the startling (e.g., loud auditory) stimulus may be needed. The stroke group with a SCM measure showed a mean difference of -96.90 ms and a 95% CI [-168.87, -24.93]. The healthy group with a SCM measure showed a mean difference of -52.73 ms and a 95% CI [-82.44, -23.02]. The stroke group without a measure of SCM showed a mean difference of -77.67 ms and a 95% CI [-111.38, -43.97]. The healthy group without a measure of SCM showed a mean difference of -30.11 ms and a 95% CI [-53.71, -6.52].

To calculate the sample sizes after subgrouping data based on the presence of SCM activity, we used mean differences between trials with and without startling stimulus, and standard deviations estimated from the CI in the subgroupings, using GPower (version 3.1.9.6) relevant statistical test (Means: Differences between two dependent means (matched pairs)), and type of power analysis (A priori: Compute required sample size – given α, power, and effect size). We found that for the stroke group, when the SCM muscle activity was present, a sample size of $n = 34$ was needed to achieve a power of 80% in a two tailed t-test with $\alpha = 0.05$, assuming a true Effect Size of 0.50. The estimated number of required participants for the healthy group, assuming a true Effect Size of 0.64, was $n = 22$. When the SCM activity was not present, for the stroke group a sample size of $n = 27$ was estimated, assuming a true Effect Size of 0.57. The estimated number of required participants for the healthy group, assuming a true Effect size of 0.45, was $n = 41$. If a one tailed t-test is used, the sample sizes

would need to be *n* = 21 for the stroke group with no SCM, and *n* = 32 for the healthy group with no SCM, respectively. The corresponding numbers for the groups with SCM would be *n* = 26 for the stroke, and *n* = 17 for the healthy group. Future studies should determine and report the range of stimulus intensities delivered during experimental protocols (due to the impact of stimulus intensity on reaction time and as reporting intensity level is depictive of what the participant is experiencing) and include trials with the presence of SCM as indicator of startle. Having SCM activity (or other reliable measures) could allow investigators differentiating with more confidence between shortened responses due to startle and trials that were shortened simply due to the effect of increased stimulus intensity (Carlsen et al., 2007).

To determine a more appropriate and effective protocol to elicit StartReact in stroke survivors, other factors such as PPI and PPF should also be considered. For example, in all studies except one (Choudhury et al., 2019), a 'warning' cue was employed and followed by an ISI before presentation of the 'go' cue. The ISI may determine if there is an inhibitory or a faciliatory effect from a *'warning'* cue on the triggered motor response due to startling stimulus (Maslovat et al., 2012). Extensive work has been done on the inhibitory effect, but little has been done on the faciliatory effect of the ISI (Aasen et al., 2005). In the included studies in the present review, the ISI varied between 1 and 3.5 s. Future studies need to determine appropriate ISI to benefit from its facilitatory effect for stroke participants.

Despite methodological differences and potential effect on the measured outcome, our review supports preservation of StartReact effect in stroke survivors. All qualified studies except one (Choudhury et al., 2019), had a relatively small sample size, and none had justified their sample size based on power calculations. Results of the present meta-analysis can therefore be used for sample size calculation in future studies that are examining StartReact effect.

3.6 Conclusion

Although the CST is the main pathway for voluntary motor control, the RetST is known to work simultaneously with and alongside the CST in some movements (Baker, 2011). The RetST is known to project to areas of the spinal cord along similar projections as the CST (Baker, 2011). StartReact literature provides evidence that the neural pathways needed to elicit a StartReact response may remain intact after stroke (Coppens et al., 2018; Honeycutt & Perreault, 2012). Furthermore, presence of StartReact effect in stroke survivors suggests remaining of the ability to preprogram (preplan) movements. Our analysis in the present review provides stronger evidence for the conclusions made by the body of research on the preservation of motor preprogramming ability and the suitability of RetST for motor rehabilitation following stroke. It also highlights the scarce amount of data in StartReact effect in the stroke population and the potential to expand research into alternate motor pathways. Future studies should investigate the effect StartReact has on movement kinematics, and furthermore if it can be used in rehabilitation.

Chapter IV Determination of Prepulse Inhibition and Prepulse Facilitation in Stroke Survivors

4.1 Introduction

Disability after stroke can range depending on the areas of the brain affected and severity of the stroke, but the most common disability that plagues stroke survivors is not being able to make voluntary motor movements (Lin et al., 2019; Maraka et al., 2014). The severity of motor impairment seen after a stroke can be determined or predicted by the amount of damage done to the CST (Maraka et al., 2014; Yoo et al., 2019). This is due to the CST being the primary motor pathway when it comes to voluntary skilled movements (Martin, 2005). The CST has multiple origination points in the cerebral cortex mostly ranging from the frontal lobe and the parietal lobe. The CST terminates in the ventral horn of the grey matter at all levels of the spinal cord, so its influence on motor control is widespread (Lemon, 2008).

It is believed that the CST has larger control over the upper limbs than the lower limbs (Jang, 2014), and there is evidence the CST has a major role in distal control of the limbs and control of fine motor skills such as Individual finger movements (Jang, 2014; Koeppen & Stanton, 2018; Mtui et al., 2021; Yoo et al., 2019). In lesions that affect only the CST, most of the fine motor control (independent finger movement) is significantly reduced, adding to the notion that without recovery of the CST motor control recovery is low (Jang 2009, 2014; Koeppen & Stanton, 2018; Martin, 2005). As seen in Lawrence and Kuypers' study (1968) in an animal where only the RetST remained as a pathway due to a lesion in the other pathways, the animal could climb its cage, but not grasp small objects. Evidence in the study of primate RetST suggests it has a stronger control of gross movements in the hand rather than individual control of the fingers (Riddle et al., 2009). Damage affecting the RetST will have different effects on motor control than damage done only to the CST.

The RetST originates in the medulla and pons sections of the brainstem (Honeycutt et al., 2013; Li et al., 2019; Mtui et al., 2021). The RetST terminates in the intermediate zone of the gray matter

between the ventral and dorsal horns (Koeppen & Stanton, 2018; Lemon, 2008). It is a motor pathway that is parallel to the CST and coincides with some termination points of the CST (Lemon 2008), making it appealing in the study of recovery after CST damage. In studies performed on macaque monkeys there is evidence of not only control of gross hand movements, but on finger control as well (Riddle et al., 2009; Baker, 2011). This is of interest in stroke research especially when combined with evidence found in monkeys after a lesion to the CST, there was a strengthening of the RetST (Zaaimi et al., 2012).

In humans, the RetST has been suggested to play a lesser role than CST in voluntary control of movement. The control is implemented via projecting to proximal muscles of the limbs and contributing to the control of posture by controlling the head, neck, and trunk (Lemon, 2008), and its involvement in locomotion and control of distal limb movements (Li et al., 2019). When a lesion occurs to the CST the RetST is likely to be left unharmed (Li et al., 2019). This suggests to investigators the RetST is a potential alternate pathway for the control of movement when the CST is damaged, not only because the RetST is likely to remain free of a lesion, but also because the pathways have similar termination points in the same areas of the spinal cord as the CST (Li et al., 2019). In support of this notion, literature provides evidence that both pathways (CST and RetST) work in tandem at the level of the hand in reaching tasks (Honeycutt et al., 2013), which makes the RetST a potential alternate pathway to the CST to target in therapy after stroke. However, more work is needed to determine if and how the RetST could be brought into action during volitional movements, and the best methodology for the effective use of the RetST in rehabilitation.

One method of evaluating functionality of the RetST and exploiting it as a means of rehabilitation by overtaking control of voluntary movement lost after stroke, is via its role in StartReact phenomenon. StartReact phenomenon is described as an involuntary response to a startling stimulus (e.g., a loud acoustic stimulus) delivered as or in association with an imperative ‘go’ stimulus that releases a preplanned movement at a shorter latency (Choudhury et al., 2019; Honeycutt & Perreault,

2012; Lee et al., 2022). StartReact phenomenon has been studied comprehensively and shown that its characteristic response begins in the reticular formation and mitigated through the RetST (Baker & Perez, 2017). In clinical conditions where there is damage or a loss of function in the CST, such as spinal cord injury, investigators have seen an increase in excitability of the RetST. This could be due to the RetST compensating for the loss of the CST function (Baker & Perez, 2017; Li et al., 2019; Zhang et al., 2022), which makes RetST a potential means for training lost movements.

Prior to exploiting RetST as a means of motor rehabilitation after stroke in a StartReact experimental context, several theoretical and methodological points should be acknowledged and/or established:

What is the evidence for intactness of RetST after stroke? StartReact reduces RT and PMT significantly, in comparison with voluntary trials in which movement is produced in response to an ordinary 'go' command (Valls-Sole et al. 1995, Carlsen et al., 2009). Original works by Valls-sole et al. (1995) first put forth the proposal the faster movement time was due to the RetST, due to the knowledge it is a pathway used in the startle reflex. Further work has been done on this theory with multiple studies suggesting a similar hypothesis (Carlsen et al., 2004a, 2004b, 2009; Carlsen & Maslovat, 2019; Honeycutt et al., 2013; Kirkpatrick 2018, Nonnekes 2014).

There is evidence that StartReact characterized by significant shortening of PMT is still producible in stroke survivors (Honeycutt & Perreault, 2012; Lee et al., 2022; Rahimi & Honeycutt, 2020). This suggests that the RetST may remain intact and can potentially be brought into action after stroke (Honeycutt & Perreault, 2012).

In traditional RT literature, RT is used to study stages of "movement preparation" of the central nervous system prior to "movement execution," and faster RT are seen as an increase in the overall central nervous system activation (Carlsen & Maslovat, 2019). Likewise, faster RT can be

seen as level of preparation leading up to the movement (Carlsen & Maslovat, 2019). This makes simple RT tests as a method of exploring the question of if the impairment in stroke survivors lies in the execution or the preparation of the movement. The use of StartReact in a RT experiment has been used as a tool to explain motor programming ability after stroke. Authors report stroke survivors are capable of planning appropriate movements, but execution of the movement is impaired as evidenced by the enhancement of muscle patterns seen in the StartReact trials (Honeycutt & Perreault 2012; Lee 2022).

What are some considerations for establishing true StartReact response? A startling stimulus is required for inducing startle reflex and StartReact effect. The presence of a startle response is commonly determined by recording increased electrical activity (EMG) in the OOC or the sternocleidomastoid (SCM). Therefore, the presence of OOC/SCM activity in startle trials in association with a drop in RT/PMT can be an indicator of true StartReact effect. The decision to use the SCM in the current study to establish a startle response is attributable to studies which argued that SCM EMG was a better option than OOC for determining the presence of startle. The reasoning is outlined in detail in Chapter 3 of the thesis. However, recent evidence (Maslovat et al., 2023) suggests that RetST can still be involved in producing a StartReact response in the presence of a startling stimulus but without observable OOC and/or SCM activity. In other words, registering OOC and/or SCM for establishing true StartReact is not necessary, and a significant reduction of RT/PMT in startle trials can be attributed to StartReact.

Effect of experimental and stimulus parameters on inhibiting or facilitating startle response and manifestation of StartReact phenomenon. Manipulation of certain experimental parameters, such as ISI can influence startle reflexes and may affect presentation of StartReact. Often when

the classical startle reflex is studied, the term PPI is used (Graham, 1975). PPI is the inhibition of amplitude of a startle response using a signal (prepulse) that has no startling effect but is presented just (typically 30 – 100 ms) before the startling stimulus. In such situations, the EMG activity (usually of OOC or SCM) observed in association with the startle 'go' signal is inhibited due to the presence of a (prepulse) signal (Maslovat et al., 2012). In contrast, PPF is where the startle reflex response amplitude is facilitated or increased by the prepulse signal that precedes the pulse signal by 1000 – 6000 ms (Aasen et al., 2005).

PPI has been extensively investigated in clinical and non-clinical human subjects; however, it has not been studied in stroke survivors. PPI has previously been used as a method of investigating psychiatric disorders that have difficulties with sensorimotor gating (Fendt et al., 2001; Maslovat et al., 2012). Sensorimotor gating, which is suggested to be the mechanism behind PPI (Zhang 2022), is the ability to filter out external input and focus on important information (Aasen et al., 2005; Braff et al., 2001; Nusbaum & Contreras, 2004; Zhang et al., 2022). Impairment of the sensorimotor gating is linked to disorders such as schizophrenia, Huntington's disease, Tourette's, and Parkinson's disease (Maslovat et al., 2012; Zhang et al., 2022). The amount of PPI an individual experiences is heavily influenced by frequency, duration, intensity, and ISI (Gómez-Nieto et al., 2020).

ISI are the timing intervals between the 'warning' and 'go' cues and have been investigated in many ways to determine PPI and/or PPF. Fendt et al. (2001) stated that the ISI that produced the strongest PPI was between 40 – 150 ms. Less work has been done on PPF than PPI, and there is discrepancy in the literature as to what ISI creates a faciliatory effect. Maslovat et al. (2012) stated that PPF of the startle reflex could occur when the ISI was between 0 – 50 ms. Gómez-Nieto et al.

(2020) and Aasen et al. (2005) stated that PPF occurred when the ISI was longer than 500 ms: specifically, an ISI of 500 – 2000 ms (Aasen et al., 2005; Graham, 1975). It has been suggested that PPI and PPF are different aspects of the same mechanism, but there is not enough research to determine if this theory is correct (Aasen et al., 2005).

When the startling stimulus is paired with a 'go' cue and a preplanned movement, and delivered after a 'warning' cue, RT and startle response may be affected (Valls-Solé et al., 2005). In StartReact experimental contexts, the effect of ISI on PMT has been studied in non-clinical participants, but there is no literature on the effect of ISI on PMT in stroke survivors. To determine what ISI should be used in a StartReact study involving stroke survivors, a study should first establish if the ISI to be used is inhibiting or facilitating the startle response.

What class of movements may lend itself better to rehabilitation via StartReact? StartReact has been studied in RT experimental contexts, where a pre-planned movement is released involuntarily in response to a startling stimulus. Under these circumstances, the role of the RetST in controlling movement may be limited to open-loop movements carried out without active feedback for the control of movement. Moreover, in stroke participants, properties of the end-effector (e.g., neural, and biomechanical properties of the limb such as spasticity and increased stiffness of the muscle-tendon units, presence of contracture) may make use of StartReact phenomenon as a means of rehabilitation of lost voluntary movements rather limited.

With these considerations in mind, the aim of this study was to determine if PPI and PPF effects were present in stroke survivors during a StartReact experiment, and to determine optimal ISI which should be used in a further StartReact study when stroke participants were involved in a goal-directed

task. Determination of appropriate ISI, i.e., intervals that facilitate StartReact or at least do not inhibit StartReact effect, would be mandatory in designing experimental StartReact studies that may be used for the rehabilitation of the lost function via engaging the RetST as AMF. For this doctoral degree, it was decided that the ISI from this study which created PPF would be used in a final study where alteration in the kinematic of movement in StartReact context would be investigated. If no ISI with PPF effect were found, ISI that induces no PPI of startle reflexes during startle trials would be used.

4.2 Methodology

4.2.1 Participants

In this study eleven participants completed the protocol, but one participant was excluded from data analysis due to a hearing impairment that was not conveyed until the day of testing. Participants were recruited into one of two groups: a clinical group which contained five participants two males and three females (ages 53-80, mean age 65 ± 10) and a non-clinical group which contained five participants two males and three females (ages 52-82, mean age 66 ± 12). Tables 1 – 2 below display participants' characteristics for the clinical and non-clinical groups. Inclusion of a non-clinical group gave the study the ability to assess potential differences in the ISI and PMTs between the two groups.

Table 1

Participants' characteristics of the clinical group

Participant	Age	Sex	Affected side	Time since stroke
201	53	Male	Left	4 years
202	80	Female	Left	3 years
203	58	Male	Left	8 years
204	63	Female	Right	6 years
205	72	Female	Right	10 years

Table 2

Participants' characteristics of the non-clinical group

Participant	Age	Sex	Dominant hand
101	58	Male	Right
102	52	Male	Left
103	62	Female	Right
104	74	Female	Right
105	82	Female	Right

Participants in the clinical group were approached and recruited from Brunel University London campus training group that was under the charity "Different Strokes". The same "Different Strokes" group leader had another training group who met at another location in London Borough of Hounslow. A letter of permission to recruit from both groups had been approved by the ethics committee. The group located on Brunel University London campus met once a week for a group therapy session and gave researchers permission to recruit from the group. Information was presented to the whole group via participant information sheets and speaking with the researcher. Interested participants were given the opportunity to ask questions to determine if they met the inclusion/exclusion criteria. Inclusion criteria for the clinical group required participants to meet the following:

- A minimum of six months post stroke
- Upper limb impairment due to stroke

- No known hearing impairment
- Able to give consent to participate and understand the instructions
- 18 years of age or older
- Ability to sit independently
- Achieve a score of two or more at the wrist on the Oxford Scale

The Oxford scale was used to measure potential participants for the clinical group muscle strength at the wrist. If the participants achieved a score of two or more and met other inclusion criteria, they were asked to join the study. On the Oxford Scale grading scale, a two is defined as "Movement of the limb but not against gravity" (Kleyweg et al., 1991). A score of two or more was decided because a participant achieving a score of two or more could complete the button press task. Other methods of recruitment consisted of emailing the flyer within personal networks and posting flyers on Brunel University London campus to recruit participants into the non-clinical group. Inclusion criteria for the non-clinical group was as the following:

- Having no known neuromuscular upper limb impairment or disability
- No known hearing impairment
- 18 years of age or older

On the day of individual data collection, and before individual data collection began, participants were given a new participant information sheet and a chance to ask questions. This refreshed their knowledge of laboratory procedures. Participants were asked to sign a consent form prior to taking part in the study.

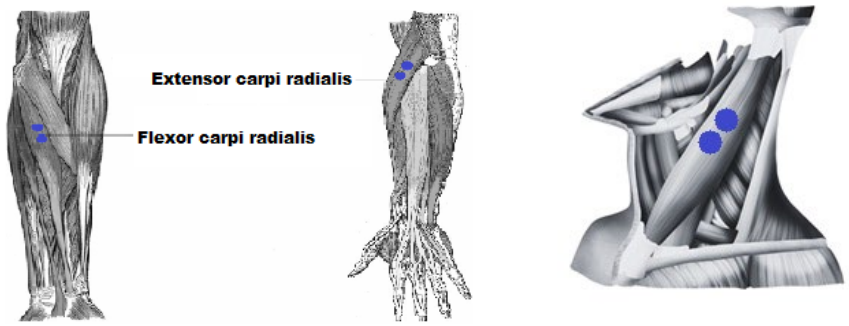
The study was reviewed and approved by Brunel University London Research Ethics Committee (UREC). Approval reference: 18927-A-Aug/2021- 33866-3

4.2.2 Equipment & Material

Trials that consisted of the auditory 'warning' signal (50 ms at 75 dB) and the visual 'go' signal were created in E-Prime software (Psychology Software Tools, Pittsburgh, PA). For the trials that contained a startling acoustic stimulus (50 ms at 110 dB), the stimulus was triggered in Spike 2 (Spike2, Cambridge, UK) and the sound intensity (dB) level was recorded using a 2400 sound level meter (TSI Incorporated) in each block. A data acquisition system (CED Power1401, Cambridge, UK) was used to record EMG from the left and right SCM and left and right flexor and extensor carpi radialis muscles at a sampling rate of (5000 Hz). EMG data were amplified 100 times by Digitimer D440-4, (Digitimer limited, Hertfordshire, UK) and recorded using bluesensor N electrodes (Ambu ltd, Denmark). Established EMG techniques as recommend by SENIAM were followed. Briefly, the recommended procedure included shaving the area, abrading using abrasive gel (Nuprep gel, Aurora, USA), and cleansing with alcohol wipes (GAMA Healthcare, Hertfordshire, UK) prior to the attachment of the self-adhesive surface electrodes. A bipolar technique was employed which involved placement of two self-adhesive active electrodes 2 cm apart center-to-center. For each muscle, a reference electrode was placed on an appropriate bony location. For the SCM the reference electrode was placed on the medial end of the clavicle. For the flexor and extensor carpi radialis the reference electrodes were placed on the lateral and medial epicondyles of the elbow.

Figure 1

sEMG sensor locations

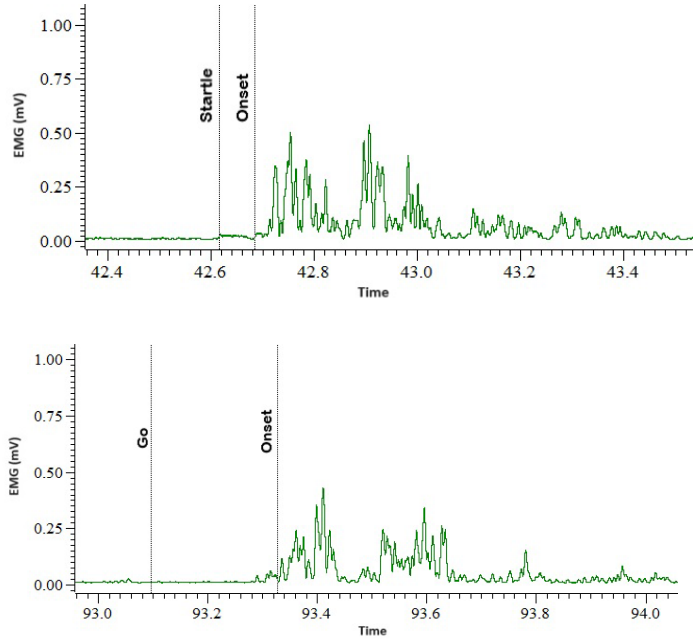


Note. Image of flexor and extensor muscles of the wrist taken from Ghapanchizadeh et al., 2015.

The data acquisition system employed a software interface from Cambridge Electronic Design Limited (Spike2, Cambridge, UK) for the recording of the EMG raw data and the generation of the startling acoustic stimulus using a sinusoid wave (500 Hz, 50 ms duration). The computer software from Psychology software tools (E-Prime, Pennsylvania, USA) was used to develop each block of trials and deliver the visual 'go' signals and the auditory 'warning' signal to the participant. To measure the time from the 'warning' signal to the 'go' signal, when signals were delivered in E-Prime, Spike2 recorded the event in a channel. On the trials where the startling stimulus was delivered (as noted above) the startle was created and marked in the Spike2 software. Muscle onset latency with respect to the 'go' or 'startle' was used to identify premotor time (PMT; Figure 2). Raw data were stored on a password protected hard drive and would be stored for a minimum of ten years from October 2022 in compliance with Brunel University London research integrity code.

Figure 2

Premotor time measurement after 'startle' and 'go' cues



Note. Top panel shows a trial where startle and go cues were paired. In the bottom panel, no startle was presented. Onset of the EMG activity was shortened (represented by the longer interval between the two vertical lines) in the top panel (see Data process and analysis below).

4.2.3. Procedure

This study measured PMT of a button press task in a simple RT experimental context that used an auditory 'warning' signal, which was followed by an imperative visual 'go' signal, to begin the response. ISI between the 'warning' and 'go' signals varied in different blocks. In random trials, the visual 'go' signals were superimposed with the startling acoustic stimulus. The startling stimulus effect on PMT was of particular interest.

Testing was conducted in the Cybex lab (HNZW032) located in the Heinz Wolff building of Brunel University London. The state of Covid-19 Pandemic at the time of experimentation required compliance with specific health and safety requirements for participants and researchers (Appendix A).

Figure 3

Design setup

Figure 3 shows the design setup used in the study. All participants were seated in a chair with their elbow propped comfortably on the table. The button was aligned with the midline of the body and a foam rest was placed underneath the elbow for comfort. Both right and left upper limbs were tested in both groups. The side tested first was decided by the participant. The participant's hand was lightly placed on top of the custom-made button without enough force to press the button.

Timeline of events in different trials was the following: in 2/3 of trials, participants received two signals, one was the 'warning' auditory signal to alert the individual to prepare to press the button and the next was the imperative visual 'go' signal to instruct the participant to press the button. Participants were asked to respond to the visual 'go' signal by pressing the button as quickly as possible. Before the testing period, ten familiarization trials were done so the participant understood the cues prior to recording. In the case of trials with the startling acoustic stimulus, the visual 'go' signal was paired with the startling acoustic stimulus. Participants were not instructed on how to react to this stimulus. The startling acoustic stimulus was emitted from a speaker located in front of the participant. In the

remaining one-third of trials, only a startling stimulus was delivered (i.e., no 'warning' and/or 'go' signals).

Therefore, the following conditions were given at random to the participants in a block of trials:

Condition 1. Warning + Go (WG: a warning signal followed by a Go signal)

Condition 2. Warning + Go + Startling Stimulus (WGS: a startling stimulus was delivered simultaneously with the Go signal)

Condition 3. Startling Stimulus (SS: no warning or Go signals)

In one block of trials there were two series (one series for short ISI and one series for long ISI; Table 3) of 12 trials each (four trials in each of the conditions 1-3 above), with eight seconds between each trial. Each block was completed six times per hand (144 trials per hand; 288 trials total). adequate rest was provided between each block by allowing the participants to indicate when they were ready to proceed to prevent fatigue.

Each block contained eight ISI (1 ISI being 1 trial) including either shorter or longer ISI (Table 3). An ISI was defined as the time interval between the auditory 'warning' and visual 'go' signals in the 8 trials that had both signals. As stated above, the other four trials in a block had no ISI because there was no 'warning' or 'go' signal (condition 3 SS). For these trials, the startling stimulus was delivered four seconds into the trial.

Figure 4

'Warning' and 'go' cues separated by ISI

Trials that tested for PPI used (shorter) 50 – 400 ms ISI. Trials that tested for PPF used (longer) ISI 600 – 2400 ms. The order of the ISI within each block was randomized.

Table 3

ISI used in all blocks

Block 1	50 ms	100 ms	200 ms	400 ms
Block 2	600 ms	1200 ms	1800 ms	2400 ms

Note. All ISI used in the study. Block one is thought to elicit PPI and block two is thought to elicit PPF.

EMG recorded from the SCM was used to determine the presence of startle, and EMG from the flexor carpi radialis muscles, the major flexors of the wrist, was used for determination of the PMT.

4.2.4. Data Processing & Analysis

EMG data from all muscles recorded was rectified and smoothed using a moving average window of 0.002 s after demeaning to remove DC offset in Spike2. Measurements used in the results included PMT from the flexor carpi radialis, and activity detected in the left and right SCM. PMT was defined as the time between onset of the visual 'go' signal (or startling stimulus) to the onset of flexor activity (for pressing the button). The onset of EMG activity was detected following a threshold-detection technique based on two SD above the mean of background activity (Figure 2). Mean background activity was calculated based on recorded activity from the muscle 50 ms prior to the 'warning' stimulus for every trial. 50 ms before a 'warning' signal was used because it was a time when no movement should be occurring, and the participant was at rest. Detection of the onset of EMG activity was then visually monitored and manually changed if an error occurred. EMG of the SCM was used to determine the presence of startle. The presence of startle was confirmed if SCM EMG activity was observed within 120 ms from the onset of startling stimulus. If SCM activity was seen, the trial was labeled SCM+ and if no SCM activity was seen the trial was labeled SCM-.

EMG data used in the statistical analysis were from the affected arm in the clinical group and the non-dominant arm in the non-clinical group. Individual participant's means were taken from each ISI block and separated into the following data points: short WGS, long WGS, short WG, long WG.

An independent samples t-test was used to compare the age ranges between the clinical and non-clinical groups. Comparisons were made using the means of WGS and WG data. All WGS data (i.e., SCM+ and SCM-) were used and compared to WG data in both clinical and non-clinical groups.

To determine the effects of startling stimulus and ISI on PMT the Wilcoxon signed ranks test was employed with adjustment of the *p* value where required. A non-parametric test was chosen due to the current study having a sample size of five clinical and five non-clinical participants. This is a relatively low sample size and no assumption with respect to the distribution of data was made.

4.3. Results

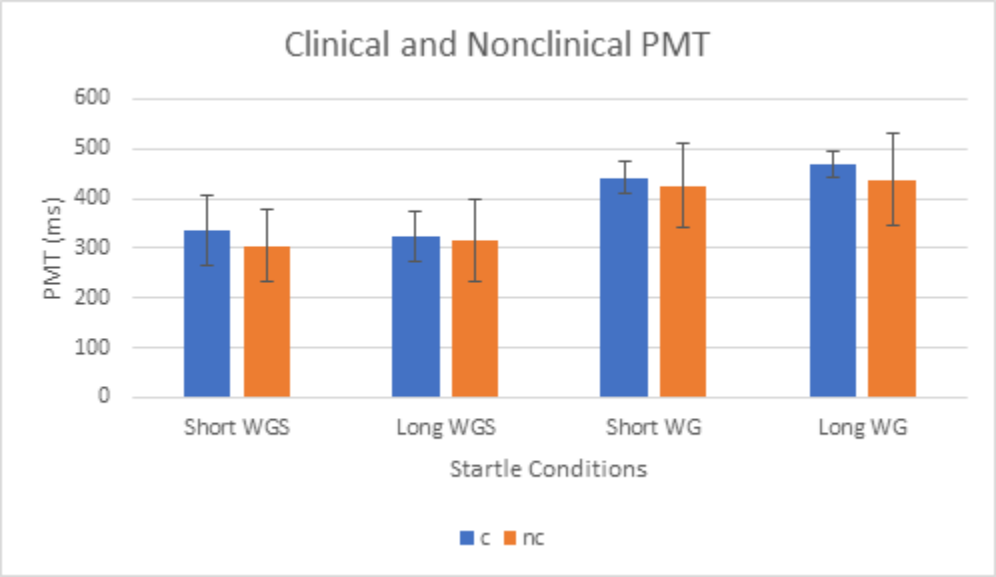
There was no significant difference in ages between the clinical and non-clinical group t (8) = 0.055, p = 0.958, two-tailed. When the data were analyzed only 4% of the trials in the clinical group were classified as having SCM activity and 17% of trials in the non-clinical group were classified as having SCM activity within 120 ms. Due to this, all results reported are PMT of non-startle trials (WG) or PMT of startle trials (WGS) regardless of SCM+/-.

4.3.1 ***Non-parametric results***

Startling stimulus reduced PMT, but ISI did not affect PMT in non-clinical and clinical participants. The results showed PMT was faster when a startling stimulus was present vs when it was not present. Figure 5 shows the mean PMT recorded from non-clinical and clinical groups in the two startling and ISI conditions.

Figure 5

Clinical and non-clinical PMT for different experimental conditions



Note. PMT recorded for both the non-clinical (NC) and clinical (C) groups under different startle (WG vs WGS) and ISI (short vs long) conditions. Group means are plotted. Error bars are ± 1 SD.

For the non-clinical group, WG PMT for the short and long ISI were 425 ± 170 ms and 438 ± 184 ms, respectively. Corresponding values for the clinical group were 441 ± 65 ms and 468 ± 53 ms. When the startling stimulus was present, WGS PMT values for the non-clinical group in the short and long ISI conditions were reduced to 305 ± 145 ms and 316 ± 167 ms, respectively. Clinical group WGS PMT were 336 ± 138 ms for the short ISI, and 324 ± 98 ms for the long ISI condition.

Results of the Wilcoxon signed rank test showed that PMT was significantly faster when a startling stimulus was present in both short (Z = -2.803, p = 0.005) and long (Z = -2.803, p = 0.005) conditions. The statistical test was run with a corrected p-value of 0.0125

Table 4

PMT values for each condition

		Short		Long	
Participant	Group	WGS	WG	WGS	WG
101	Non-clinical	163	221	133	196
102	Non-clinical	480	606	540	596
103	Non-clinical	404	556	395	617
104	Non-clinical	152	276	172	303
105	Non-clinical	323	465	339	478
201	Clinical	228	421	216	482
202	Clinical	201	375	301	430
203	Clinical	483	512	441	517
204	Clinical	284	391	252	397
205	Clinical	485	507	409	511

Note. PMT are reported in ms.

Results of the Wilcoxon signed rank test showed the effect of ISI on PMT was nonsignificant in WGS (Z = -0.255, p = 0.799) or WG (Z = -1.784, p = 0.074) conditions which indicated there was no difference to PMT when the ISI was shorter or longer.

4.4 Discussion

The main aim of the current investigation was to determine the effect of ISI on prepulse inhibition and prepulse facilitation in a StartReact study and find the optimal ISI for facilitating StartReact in stroke survivors. This is the first study to examine PPI/PPF effect in such a context. Having the data to show if specific ISI influence releasing a preplanned motor task is imperative in designing studies that explore the use of StartReact experimental context as a means of motor rehabilitation after stroke. Based on currently available literature, it was expected that presence of a LAS, delivered simultaneously with a visual 'go' signal, would shorten PMT in clinical and non-clinical populations. However, the effect of the ISI on facilitating or inhibiting PMT and release of the preplanned movement (presumably through RetST) in stroke survivors had not been studied before. Results indicated the ISI had no effect on the PMT. The results were in line with previous literature that report acceleration of

PMT by showing a significant effect of trials with a startling stimulus being faster than trials without a startling stimulus in both clinical and non-clinical groups. The results also give an indication that this knowledge extends to the wrist flexor muscles in a button-press task but requires more data to further explore.

Separation of SCM+ and SCM- trials was initially decided based on a methodological consideration that only the former was representative of true startle effect during experimentation. However, all trials involving LAS were grouped together under WGS for the final analysis. There were two reasons for this:

- From a theoretical perspective, there are countering arguments on whether presence of SCM EMG determines a true startle effect, and therefore an examination of the differential effect of ISI on PPI/PPF in trials with or without SCM was needed. PPI is seen as a method to modify the startle reflex. In an exploration into PPI, Maslovat et al. (2012) found in trials where the ISI was 100 ms the startle reflex response (determined by the amplitude of the SCM activity) decreased but the RT remained the same. Maslovat et al. (2012) suggested the lack of changes seen in RT supported the notion that startle reflex and StartReact were controlled by two different neural pathways. Using the SCM as a determinant of true startle is common across the literature (Rahimi & Honeycutt, 2020; Carlsen et al., 2009: Ossanna et al.,2019). Carlsen et al. (2007) found the trials with SCM activity had significantly faster RT than the trials without it. Authors used this as justification for using SCM activation as the indicator startle was present and the shortened RT was not due to stimulus intensity effect. The common conclusion, arguing in favor of SCM+ trials for true startle effect has been the association between the fastest RT/PMT and SCM activity during experimentation.

In contrast to this point of view, a recent study completed by Maslovat et al. (2023) they suggested the observed SCM activity or lack of activity did not necessarily mean StartReact was or was

not present but could be an indicator for the level of contribution and amount of RetST output seen in the trial leading to a robust StartReact effect. Carlsen et al. (2007) reported premotor RT for trials with "no response indicator" and "startle response indicators with OOC or SCM". The data for trials with no response indicator reached what authors termed asymptote at 113 dB. At this threshold, the premotor RT did not get any faster with an increase in stimulus intensity to higher values of 123 dB. Any faster PMT over the 113dB threshold could be due to the StartReact effect, and the premotor RT that are significantly faster when seen with SCM activity could be due to the increased level of activation in RetST as theorized in Maslovat et al. (2023).

- Of less importance was a practical point due to the low number of SCM+ trials, the required data was not available to examine the effect of manipulating ISI on PPI/PPF separately in SCM+ and SCM- trials between the two groups of participants. Previous protocols with an EMG measure of the right and left SCM muscle in each participant were followed. However, as reported in the Results section, only 4% of the trials in the clinical group were classified as having SCM activity and 17% of trials in the non-clinical group were classified as having SCM activity within 120ms. Due to the low percentage of trials showing SCM activity and the more recent argument questioning if SCM is an indicator of startle, SCM+ and SCM- data was combined for WGS trials.

In non-clinical participants, when a startling stimulus is presented in association with a 'go' signal, and with a preplanned movement ready to be executed, PMT of the relevant muscles are shorter than normal. After a stroke, researchers have queried if ability to plan a movement is decreased. The ability to elicit faster RT and PMT after stroke shows there is motor programming ability, but perhaps a lack in ability to execute the movement voluntarily (Honeycutt & Perreault, 2012;). The observed reduction in PMT in the current study aligns with prior research suggesting retained motor programming ability post-stroke. Additionally, it implies potential for utilizing RetST as an AMF for motor execution

after stroke and provides an argument for building upon previous work to flexors of the wrist in a button-press task.

The RetST being involved in StartReact has raised an interest in motor rehabilitation after stroke, due to the possibility that the RetST could be spared from injury and used in movement execution. The hand is often a major impairment after a stroke, and this is due to the CST having most control over the hand and fingers (Mawase et al., 2020). However, recent work shows that the RetST projections extend to the hand, but the RetST is known to have more widespread projections rather than projections that are selective enough to control fine motor skills (Baker, 2011). Honeycutt et al. (2015) demonstrated the RetST has some control over the hand in their study by investigating StartReact in a hand extension task. The results from the current study expand on Honeycutt et al., (2015) results by suggesting StartReact can also be found in a wrist flexion task by reporting a faster PMT in the wrist flexors when a participant completed a button press task. The hand is often a focus in rehabilitation after a stroke due to its importance in everyday living (Barry, 2022). If StartReact can be elicited in hand movements in a larger population of stroke survivors, it has the potential to be a rehabilitation method, but some methodological issues for training participants in a StartReact context need to be addressed first.

Investigations into StartReact use a 'warning' cue and a 'go' cue with a predetermined ISI, i.e., the time interval between a 'warning' and the LAS time, that is predominantly between 1.5 – 3.5s (Carlsen et al., 2004a, 2009; Honeycutt et al., 2013, 2014, 2015; Lee, 2022; Rahimi, 2020). This time is used to prevent anticipation of the startling noise and to prevent the risk of PPI. PPI in the startle reflex literature is primarily seen in protocols with ISI between 30 – 500 ms (Braff et al., 2001; Maslovat et al., 2012) hence in the current study the use of two blocks of ISI: short ISI being 50 – 400 ms and long ISI being 600 – 2400ms.

The results showed there were no significant effects seen on PMT in either short or long ISI groups in our participants. The lack of a significant effect of ISI on PMT under present experimental

context, suggested no optimal ISI between 50 and 2400 ms for facilitating StartReact or at least not inhibiting it, in our population of stroke survivors. This knowledge will be used in a follow up study, for the current thesis, which will investigate movement kinematic in a reaching task after stroke in a StartReact context. The next study will utilize a similar protocol with similar inclusion criteria to the current study except the ISI will be a predetermined time that is in line with the literature.

4.5 Limitations

The clinical group only consisted of individuals who could achieve a two or more on the Oxford scale. This was due to the requirement of having the ability to press the button in the task. This limits generalizability of the results by excluding participants who are severely affected at the wrist. Future studies should look at all levels of impairment in stroke, and whether alteration in the latency of muscle activation is affected by the ability to execute movement. Additionally, the trials were randomly selected by the computer software with no ability to control if trials with a startling noise were presented consecutively. In future studies the trials with a startling noise should be spaced apart to prevent habituation of the noise. In analyzing the results, all PMTs were recorded with no upper or lower limit. Not having an upper limit of PMT includes trials where the participant was potentially inattentive to the task. This would increase the overall means of the PMT. The results from this study are based on a sample size of ten with five participants in each group. This gives an indication that this methodology can be used in the stroke population but would require more participants to have a higher power.

Chapter V StartReact Influences Upper Limb Kinematic and Endpoint Accuracy in Reaching

5.1 Introduction

As stated in the previous chapters, upper limb impairment is a leading cause of functional disability after suffering a stroke. Kinematic changes in the impaired upper limb after stroke include limitation in the available range of movement and altered joint coordination manifested by inflexibility in synergies formed (Reisman & Scholz, 2006). These changes, in addition to the altered muscle activation patterns, are primarily due to the neurological impairment caused by the stroke (Reisman & Scholz, 2006). Changes in joint coordination can involve shoulder, elbow, wrist, and interphalangeal joints of the fingers and lead to impaired or atypical synergies formed during upper limb movements (Shirota et al., 2016). Various methods are used to quantify movement patterns after stroke such as functional assessments, goniometry, motion analysis, EMG, and robotic devices. The ability to quantify the movement patterns is essential in rehabilitation research and using a combination of these methods allows for a thorough assessment of the affected limbs movement patterns and their response to therapeutic interventions (Shirota et al., 2016).

Two measures of movement execution commonly seen in stroke literature are endpoint accuracy and coordination variability (van Emmerik et al., 2016). Using endpoint accuracy as an outcome measure of the underlying coordination patterns, a movement is argued to be more functional if the movement is faster, and more accurate with a lower level of endpoint variability (Tomita, 2017; Van Emmerick et al. 2016). However, decreased endpoint variability is not necessarily indicative of associated decrease in coordination variability (Van Emmerick et al. 2016). For example, an increase in coordination variability is associated with the ability to execute a task in various ways. On the other hand, increased endpoint variability is indicative of poor endpoint accuracy (Van Emmerick et al. 2016). Overall, the quality of movement outcome can be determined by endpoint accuracy, while endpoint accuracy in turn emerges

as an outcome of the joint/segment coordination within the synergy formed (Tomita et al. 2017). Kinematic changes of the upper limb in chronic stroke survivors lead to a movement that is lacking in flexibility (i.e., is stable). Stable or rigid systems are representative of a motor system with a reduced amount of variability (Stergiou & Decker, 2011). The reduction in variability can occur at different levels of analysis and a reduction of coordination variability at the joint/segment level of the upper limb can be associated with a lack of endpoint accuracy in hand functions characterized by increased endpoint variability in goal-directed tasks (Cirstea & Levin, 2000).

From the perspective of DST, system variability, or the ability to change the coordination patterns between segments/joints is an important feature of the neuro-motor control mechanisms (Stergiou & Decker, 2011). The theory of optimal movement variability proposes that the amount of variability seen in the motor system is an indicator of the system's health. According to this viewpoint, all healthy systems contain an optimal amount of variability that produces a movement that is adaptable in interacting with the environment, and deviations from the optimal amount of variability, whether it is an increase or decrease, negatively affect outcome of the ongoing movement (Stergiou et al., 2006). As mentioned above, motor systems in chronic stroke survivors display a decrease in variability and the resultant movements are rigid/stable. Following the theory of optimal movement variability, post-stroke movements may be perturbed to increase the amount of joint/segment variability to prompt a change in which new movement patterns arise that could be more functional and with improved endpoint accuracy.

With the CST being compromised after a stroke, the question of whether improvements in function in chronic stroke survivors are due solely to plasticity of the CST or increased activity of other neural pathways remains to be determined. Animal studies on motor pathways have shown an increase in the RetST control of voluntary movements after CST damage (Van Lith et al., 2018). The RetST has

similar projections to the spinal cord as the CST and the RetST exert some control over proximal and distal portions of the limbs (Baker, 2011, Riddle & Baker, 2010). An increase in RetST activity following reduced activity in CST is therefore expected.

Methods of studying the RetST in humans stem from the StartReact and startle reflex literature. As mentioned in previous chapters StartReact is the accelerated release of a programmed movement in response to a startling stimulus (Carlsen et al. 2012; Honeycutt et al., 2013, 2015; Lee et al., 2022). Preservation of StartReact phenomenon has been established in clinical and non-clinical populations (Carlsen, 2004; Nonnekes et al., 2015; Rahimi & Honeycutt, 2020). In StartReact research, stroke population and their motor responses to the startling stimuli are a specific area of interest due to the impairment of the CST and potential of the RetST to be spared. Using StartReact as a method of triggering the RetST may have some promises in neurorehabilitation through recruiting alternate motor pathways. It is of clinical importance to determine if recruitment of alternate motor pathways such as RetST in StartReact experimental contexts, may lead to a more functional movement than can be accomplished using the remnants of the CST in stroke survivors.

Previous studies have reported that in startle trials kinematic measures and endpoint accuracy do not change when compared to control movements (Carlsen et al., 2004, 2011; Rahimi & Honeycutt, 2020). The lack of change in endpoint accuracy led some researchers (Rahimi & Honeycutt, 2020) to surmise that StartReact does not show an improvement in functional movements. The measurements employed were often movement time, peak displacement, and angular velocity. There are multiple studies that explore the kinematic change in StartReact by analyzing single-joint (Castellote & Valls-sole, 2015; Cressman et al., 2006; Honeycutt and Perreault, 2012; Honeycutt et al. 2015; Maslovat et al., 2011) or multi-joint movements (Ossanna et al., 2009; Lee et al. 2022; Rahimi & Honeycutt, 2020). None of the previous studies, however, have completed an analysis of an unconstrained upper limb reaching

task. Constraining movements in these studies may have masked potential effect of startling stimuli on increasing movement variability and its beneficial effect on movement accuracy.

The aim of this study was to determine if an alteration in movement kinematic or endpoint accuracy could be seen when a startling stimulus was involved in an unconstrained reaching task. For reaching tasks, it was hypothesized that improvement in function may take the form of improved endpoint accuracy executed with new (altered) movement coordination patterns characterized by increased variability at the joint/segment level.

5.2 Methodology

5.2.1 *Participants*

Thirteen participants were recruited for the study. As in Chapter 4, participants were recruited into two groups: a clinical group which contained six participants three males and three females (age range 45 – 82 years; Mean ± SD age: 63 ± 13 years) and an age-matched non-clinical group which initially contained seven participants. One participant in this group opted not to continue with the session due to the stimulus being frightening. Therefore, the final non-clinical group had three males and three females (age range 47 – 73 years; Mean ± SD age: 58 ± 9 years). Tables 1 and 2 display participants characteristics for the non-clinical and clinical groups, respectively.

Table 1

Participants' characteristics of the non-clinical group

Participant	Age	Sex	Dominant hand
111	52	Male	Left
112	47	Male	Right
113	73	Male	Right
114	55	Female	Right
115	62	Female	Right
116	59	Female	Right

Table 2

Participants' characteristics of the clinical group

Participant	Age	Sex	Affected side	Time since stroke
211	54	Male	Left	4 years
212	45	Female	Right	8 years
213	59	Male	Left	9 years
214	72	Female	Right	9 months
215	82	Male	Left	5 years
216	67	Female	Left	1 year

Participants in the clinical group were first recruited by contacting the participants who took part in the study for Chapter 4 and gave consent to be contacted for future studies. Further recruitment was done from the Different Strokes charity group used in Chapter 4. Information was presented to the whole group via participant information sheets and speaking with the researcher. Interested participants were given the opportunity to ask questions by researcher to determine if they met the inclusion/exclusion criteria. Inclusion criteria for the clinical group required participants to meet the following:

- A minimum of six months post stroke
- Upper limb impairment due to stroke
- No known hearing impairment

- Able to give consent and understand instructions
- 18 years of age or older
- Ability to sit independently
- Normal or corrected to normal vision

In the study reported in Chapter 4, a muscle strength measurement was used due to the requirement for an ability to press the button used in the study. This experimental study did not use a muscle strength measurement in the current study due to the task being a 'reaching task'. Inclusion criteria for the non-clinical group were as the following:

- Having no known upper limb impairment or disability
- No known hearing impairment
- 18 years of age or older
- Normal or corrected to normal vision

No clinical participant who was willing to take part in the study was excluded due to inability to extend fingers or having limited range of motion at the three main joints of the upper limb. The reaching task itself had a low index of difficulty to encourage movement (below).On the day of individual data collection, and before individual data collection began, participants were given a new participant information sheet and a chance to ask questions. This refreshed their knowledge of laboratory procedures. Participants were asked to sign a consent form prior to taking part in the study.

The study was reviewed and approved by Brunel University London Research Ethics Committee (UREC approval reference: 39806-MHR-Nov/2022- 41982-2).

5.2.2 ***Equipment & Materials***

All equipment and materials remained the same in this study as used in Chapter 4. Trials with an auditory 'warning' sound used a tone burst for a duration of 50 ms at a sound level of 75 dB, and those containing a startling stimulus used a tone burst for 50 ms at a sound level of 113 dB to this effect.

The previously reported data acquisition system was used to record EMG from the left and right SCM, and the triceps brachii long head of the arm used for reaching. Reference electrode for the triceps brachii long head was placed on the olecranon. For all EMG techniques, materials used, and information on recording of data, see section 4.2.2.

Kinematics of the movement were measured using ten cameras in Qualisys motion analysis system (Göteborg, Sweden) operating at 120 Hz sampling rate. The marker set consisted of 28 reflective markers placed on the upper limb and trunk. The movements of the hand, forearm, upper arm, shoulder, and thorax were measured using the marker system. The list of markers was as follows:

RAIC	Right anterior iliac crest
RPIC	Right posterior iliac crest
LAIC	Left anterior iliac crest
LPIC	Left posterior iliac crest
IJ	Incisura Jugularis – suprasternal notch
PX	Processus Xiphoideus – the xiphoid process
C7	Spinal process of the 7th cervical vertebrae
T8	Spinal process of the 8th thoracic vertebrae
AI	Inferior angle of the scapula
TS	Root of the scapular spine
AA	Acromial Angle (part of Acromial Cluster)
AC2	Acromial Cluster 2
AC3	Acromial Cluster 3

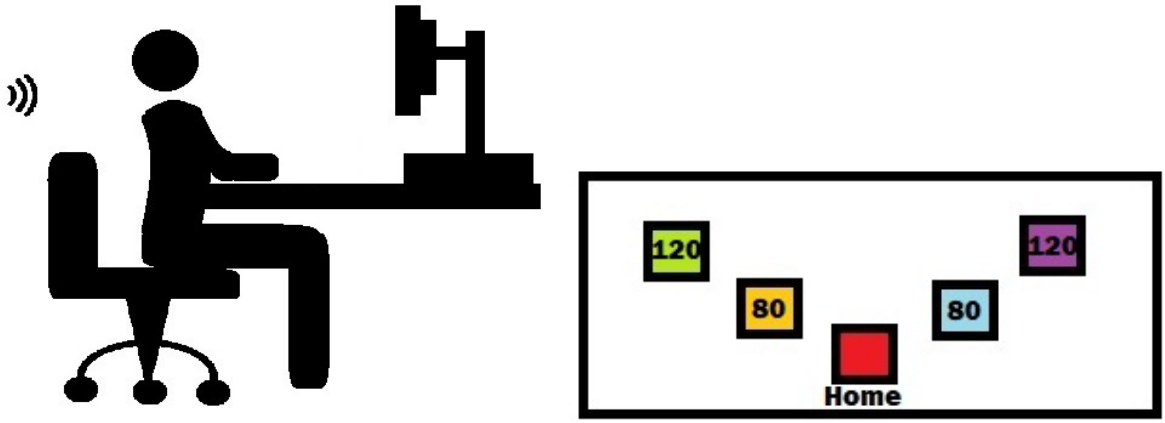
UA1	Upper arm Cluster 1 (proximal to UA2 and UA3)
UA2	Upper arm Cluster 2 (medial and distal to UA1)
UA3	Upper arm Cluster 3 (lateral and distal to UA1)
ME	Medial epicondyle
LE	Lateral epicondyle
FA1	Forearm Cluster 1 (proximal to FA2 and FA3)
FA2	Forearm Cluster 2 (lateral and distal to FA1)
FA3	Forearm Cluster 3 (medial and distal to FA1)
RS	Radial styloid process
US	Ulnar styloid process
H1	Hand Cluster 1 (distal to H2 and H3)
H2	Hand Cluster 2 (thumb side of the hand)
H3	Hand Cluster 3 (5th metacarpal side of the hand)
F2	Distal end of 2nd metacarpal
F5	Distal end of 5th metacarpal

5.2.3 *Procedure*

This study measured PMT of the triceps brachii long head and kinematic of the arm of a reaching task in a StartReact experiment. For the clinical group the affected arm, and for the non-clinical group the non-dominant arm was used in testing. All testing was conducted in the Biomechanics lab located in the Heinz Wolff building of Brunel University London (HNZW036). The design setup illustrated in Figure 1 was similar to that of used in Chapter 4 but did not use a button and instead had 4 target locations on a table.

Figure 1

Design setup



Participants were seated in an office chair (unless wheelchair bound) with their elbow and forearm resting comfortably on the table in such a position where their hand was aligned with the midline of their body. This position was labelled 'home' as seen in red. The other locations on the table were 'targets' (see text for description of targets). Startling Stimulus was delivered via speakers located behind the participant.

As in Chapter 4, standard trials consisted of two types of signals, one was the 'warning' auditory signal to alert the individual to prepare to move and the next was the imperative visual 'go' signal to instruct the participant to move. 'Warning' and 'go' signals were separated by an ISI between 1500 – 2500 ms. ISI was chosen randomly by the computer software to prevent anticipation of the 'go' cue. The range was chosen due to the previous study illustrating the ISI had no effect on PMT and this range is known to have a facilitation effect on startle and is more likely to produce anticipatory attention. Participants were told when the 'go' signal was given they were to move as quickly and as accurately as possible to the center of the target. At random trials, the 'go' was paired with a loud auditory stimulus but participants were not instructed how to react to the stimulus. Prior to completing the protocol participants were given ten familiarization trials to understand the cues.

Three conditions were delivered at random for each participant:

Condition 1. Warning + Go (WG: a warning signal followed by a Go signal)

Condition 2. Warning + Go + Startling Stimulus (WGS: a startling stimulus was delivered simultaneously with the Go signal)

Condition 3. Startling Stimulus (SS: no warning or Go signals)

A total of 104 trials were run, separated into eight blocks of thirteen trials. Each target was tested with two blocks of trials (26 trials per target). The order the targets and blocks were presented to participants were randomized using Microsoft Excel. Each block consisted of nine WG trials, three WGS trials, and one SS. The setup allowed for no WGS trials to be delivered consecutively. Between each block adequate rest was given by allowing the participant to indicate when they were ready to proceed to prevent fatigue.

At the beginning of data collection, the participants 'home' target was determined by the participant comfortably resting their forearm on the table with their elbow at 90° flexion and their hand visually aligned with the midline of the body. Participants were instructed this location was where they were to begin and end all movements.

The participant's workspace was created by finding a maximum reach ipsilaterally and contralaterally (with respect to the moving arm). For the clinical group, the affected arm was stretched passively, in both directions, without involving the trunk to a point at which they felt was their maximum reach without causing discomfort. The non-clinical group was instructed to stretch to their maximum reach ipsilaterally and contralaterally without involving their trunk. A 90° angle from the 'home' target point was used to guide the participants in the correct direction.

There were four targets in total located at either 80% or 120% of the participant's maximum reach ipsilaterally or contralaterally. Targets were paper targets to prevent the participant from changing their movement pattern to land in the target center. Movement amplitude was defined as the

distance between the 'home' position and the center of the target. The target size was relative to each participant's movement amplitude. Targets at 120% of the maximum reach were accordingly larger in size than targets at 80% of the maximum reach. This was determined using an index of difficulty. An index of difficulty was used to ensure the level of difficulty was standard across all participants and targets. An index of difficulty of 2 (ID = 2) was used. (Fitts) Index of difficulty, which was used in this study, is a measure of difficulty in completing a target reaching task and is calculated as a logarithmic ratio between movement amplitude (A) and target diameter (D) (ID = log_2(2A/D)). Table 3 below outlines a participant's maximum reach, target locations, and target size from the ID=2.

Table 3

Maximum reaches and target information

Participant	Maximum Reach		Target Locations				Target Size (cm)			
	Ipsilateral	Contralateral	Ipsilateral		Contralateral		Ipsilateral		Contralateral	
			80%	120%	80%	120%	80%	120%	80%	120%
211	48	31	38	58	25	37	19	29	13	19

5.2.4 *Data Processing & Analysis*

All non-clinical participants who completed the data collection were included in data analysis. The participant who chose not to continue with data collection was not included due to the limited amount of reaching movements completed before choosing not to proceed. One clinical participant (Participant 215) was excluded from kinematic measurement analysis due to his inability to control the end of the movement. The participant's movement consistently exceeded the target locations, and he was unable to complete the reaching task as instructed.

As stated before, muscle activity was measured using EMG recorded from the triceps brachii long head and the right and left sternocleidomastoid muscle. All EMG processing and analysis was repeated from Chapter 4 including techniques in removing DC offset, smoothing, rectification and determining background activity in Spike2. As in Chapter 4 premotor time was measured as the time

between the visual ‘go’ or auditory stimulus and the onset of triceps muscle activity. Muscle activity seen in the SCM was noted to follow previous studies methodology but was not used as an indicator of startle. SENIAM recommended techniques were followed for skin preparation and sensor location and outlined in Chapter 4.

Motion capture data were filtered with a low-pass, butterworth filter with a frequency of 5 Hz. Qualisys tracking manager (Göteborg, Sweden) was used to fill gaps in marker trajectories during data collection. Motion data were exported in .c3d format and analyzed in Visual 3D (C-Motion, Washington, DC, USA). Coordinate systems and segment rotations used in the model were generated following ISB guidelines for the upper limb (Wu et al., 2005). Visual 3D was used to measure joint angles and velocities of the shoulder, wrist, elbow and thorax, and movement time. Joint angles from Visual 3D were time normalized and used to determine range of motion (ROM) and create angle-angle diagrams of the wrist-elbow in both clinical and non-clinical groups for the duration of the reach which was defined as the start of the movement to the most extended position. Angle-angle diagrams were calculated using a randomly chosen six trials in the WG condition. This was to ensure the number of trials in each condition was the same. All joint angles used and reported in the present study were flexion/extension movements. ROM was defined as the difference between the smallest and the largest joint angle during the reach. Onset of each movement was found by a sustained rise in the velocity of the hand of >= 30 mm/s for 100 data points above velocity of the hand at rest (i.e., 0 mm/s). Maximum reach was determined at the point where the hand was furthest from the shoulder. Movement time was measured as the time from the onset/start to maximum reach.

CRP was used as an additional measure of coordination to angle-angle diagram.

$$CRP = \theta_{distal} - \theta_{Proximal}$$

where θ_{distal} and $\theta_{Proximal}$ refer to the phase angle of the distal and proximal joints, respectively. Phase angles (θ_{angle}) were calculated using the arctangent of angle (X_i) vs velocity (Y_i) at any moment of time.

$$\theta_{angle} = \tan^{-1}\left[\frac{Y_i}{X_i}\right]$$

An average CRP was calculated from the time normalized WGS trials and WG trials and used in the study. CRP values were presented in a graph format for each of the four target locations and two stimulus conditions to descriptively assess differences with the corresponding curves in the WG condition for the non-clinical participants (considered as the standard condition). SD of the CRP values for these trials was calculated and an independent samples t-test was used to examine as a measure of alteration in the pattern of coordination due to the introduction of the SS.

Endpoint accuracy measurements were completed following Kim et al., (2000). The guidelines on measurements included radial error (RE), adjusted variable error (AVE), total spread of error (TSE), and directional error (DE); however, only AVE was relevant to the current study. The above measurements were created for investigations that consisted of assessing two-dimensional (2D) accuracy which could therefore lend itself to the current investigation. In the present study, the marker used to calculate endpoint accuracy was the F2 marker located on the distal end of the 2nd metacarpal. For the calculation of the endpoint accuracy maximum reach (Max Reach) was first determined at which point the hand was furthest from the shoulder. Then, the 2D coordinates of the F2 marker were taken from the location of max reach and used in the calculation of measures of endpoint accuracy. To this end, the endpoint coordinates were run through a custom MATLAB (version 9.14.0 (R2023a), Mathworks Inc.) code that produced AVE and the endpoint plots. The following formula was used in the calculations:

$$AVE = \frac{1}{n}\sum_{i=1}^{n}\sqrt{(x_i - \bar{x})^2 + (y_i - \bar{y})^2}$$

where $x_i, y_i, \bar{x}, \text{and } \bar{y}$ refer to horizontal (mediolateral and anteroposterior) coordinates of the F2 marker as observed in the plane of table, and means of these coordinates, respectively. n was the number of endpoints used in these calculations.

Although Kim et al. (2000) recommended TSE (area over which endpoints were spread) to be used as total variability of the reaches by calculating the area between the reaches, the startle trials were 30% of the total number of reaches making the number of reaches between WGS and WG inconsistent. Accordingly, measures of TSE would be affected by the unequal number of trials used in the calculation of TSE between the two stimulus conditions. Therefore, AVE was the sole measure of endpoint accuracy in the present study.

A two-tailed independent samples *t*-test was used to compare the mean age of both groups and showed there were no differences between the clinical and non-clinical groups. To determine the effect of startling stimulus on PMT, AVE, and ROM the non-parametric Wilcoxon signed ranks test was used due to the small sample size and no assumption with respect to the distribution of data was made. In all analysis the term startle was used as the startling stimulus condition comparing the WGS group to the WG group. SPSS (29.0.1.0 (171), IBM) was used for the analysis. Level of significance for alpha was 0.05.

5.3 Results

In the following results, reported means in conditions WGS or WG were comprised of trials from all 4 targets (120C, 80C, 120I, 80I) pooled together unless stated otherwise, because the main purpose of the present study was to examine possible effect of StartReact on altering kinematic of the reach. Therefore, trials were pooled together for the analyses completed on premotor time and movement time since all target conditions were presented to all participants, and ID was kept consistent at two which did not discourage movement nor required forming different (segment/joint) synergies for

completion of the task. It is important to note an independent samples t-test showed there was no significant difference in ages between the clinical and non-clinical groups ($t_{(10)} = -0.789$, $p = 0.448$, two-tailed).

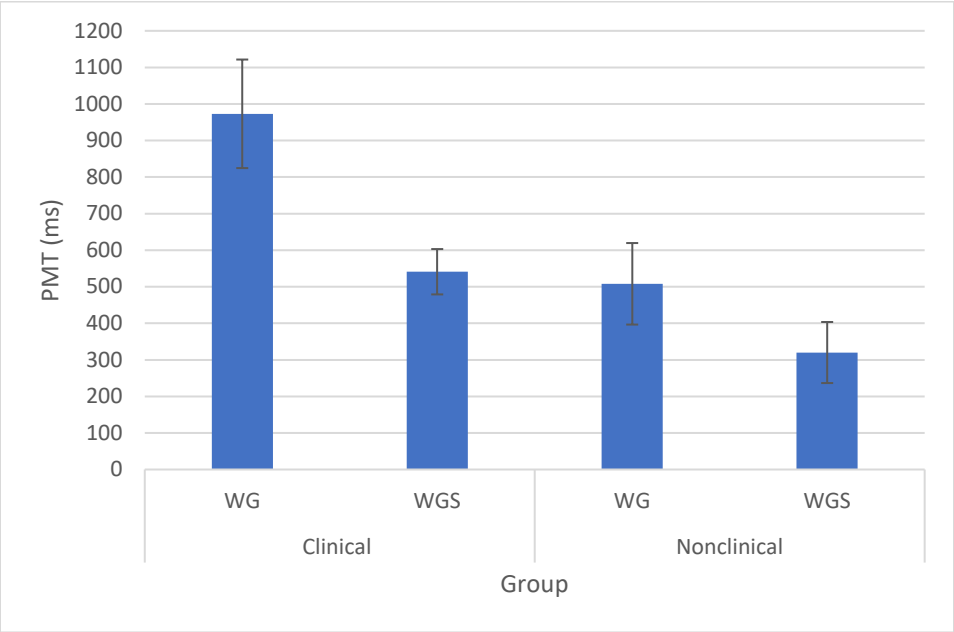
5.3.1 *PMT and movement time*

5.3.1.1 Non-Parametric results.

PMT and movement times were compared between WGS vs WG conditions to assess the effect of startle on the onset and execution time of the response and argue for the possible involvement of an alternate neural pathway in producing the response. PMT in startle conditions were significantly faster in both clinical and non-clinical groups. Figure 2 illustrates the mean PMT seen in both groups and both conditions.

Figure 2

Mean PMT for non-clinical and clinical groups



Note. PMT recorded for the non-clinical (NC) and clinical (C) groups under different startle (WG vs WGS) conditions. Group means are plotted. Error bars are ± 1 SD.

For the non-clinical group values (M ± SD) were: WG PMT 508 ± 223 ms; WGS PMT 320 ± 167 ms. PMT for the clinical WG were 973 ± 297 ms and WGS PMT were 541 ± 124 ms. Results of the Wilcoxon signed rank test showed a significant decrease in PMT (Z = -2.803, p = 0.005) when a startle was present.

Table 4

PMT values for each condition

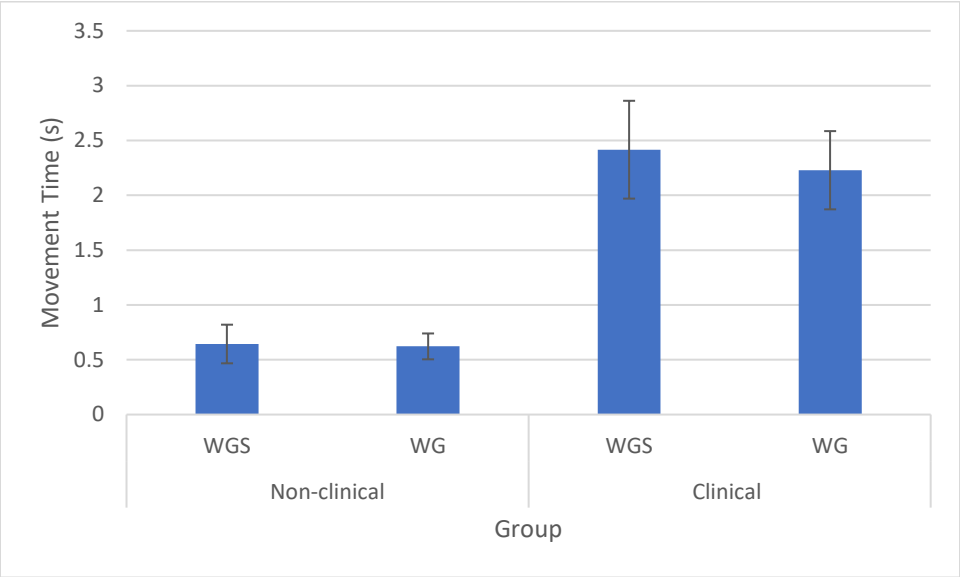
Participant	Group	WGS	WG
111	Non-clinical	0.265	0.424
112	Non-clinical	0.527	0.824
113	Non-clinical	0.524	0.702
114	Non-clinical	0.147	0.262
115	Non-clinical	0.284	0.536
116	Non-clinical	0.174	0.302
211	Clinical	0.475	1.007
212	Clinical	0.385	
213	Clinical	0.725	1.134
214	Clinical	0.499	1.204
215	Clinical	0.464	0.545

Note. PMT are reported in seconds.

Movement time was recorded to determine if the total execution time of movements, which were expected to have a shorter PMT when the startle was present, would also be affected by the presence of the stimulus. Movement time in both conditions was faster in the non-clinical group, as expected (figure 3). In the WGS and WG conditions both groups produced similar movement times. Figure 3 shows the movement times seen in the two groups and stimulus conditions. Results of the Wilcoxon signed rank test showed movement times were not significantly affected by the startle condition (Z = -1.334, p = 0.182).

Figure 3

Mean movement times for non-clinical and clinical groups



Note. Movement times recorded for the non-clinical and clinical groups in both WGS and WG conditions are reported in s. Group means are plotted. Errors bars are ± 1 SD. For the non-clinical group, WG movement times (M±SD) were 0.622 ± 0.235 s, and WGS movement times were 0.644 ± 0.352 s. Corresponding values for the clinical groups were 2.23 ± 0.714 s for the WG and 2.42 ± 0.892 s for WGS.

Table 5

Movement time values for each condition

Participant	Group	WGS	WG
111	Non-clinical	0.514	0.649
112	Non-clinical	0.924	0.788
113	Non-clinical	1.231	1.000
114	Non-clinical	0.392	0.400
115	Non-clinical	0.395	0.481
116	Non-clinical	0.406	0.418
211	Clinical	1.577	1.728
212	Clinical	1.646	1.466
213	Clinical	3.480	3.181
214	Clinical	3.239	2.738
215	Clinical	2.137	2.031

Note. MT are reported in seconds.

Table 6

Movement times at each target

	120C	120I	80C	80I
Clinical WGS	2.2	2.5	2.5	2.6
Clinical WG	2.1	2.5	2.0	2.3
Non-clinical WGS	0.7	0.6	0.7	0.5
Non-clinical WG	0.7	0.6	0.6	0.6

Note. All movement times in each group separated into targets. Across each group movement times were similar due to the ID of 2 regardless of target location. Times are displayed in s.

5.3.2 *Endpoint Accuracy*

5.3.2.1 Non-Parametric results.

Endpoint accuracy was measured to determine if the accuracy for the participants' reach changed between the WGS and WG conditions. Alteration in endpoint accuracy was assessed using AVE which represents endpoint variability around each participant's own mean endpoint. A Wilcoxon signed

rank test found endpoint variability was significantly decreased (Z = -2.134, p = 0.033) when a startle was involved which supported improved accuracy in StartReact responses.

Table 7

AVE values for each condition

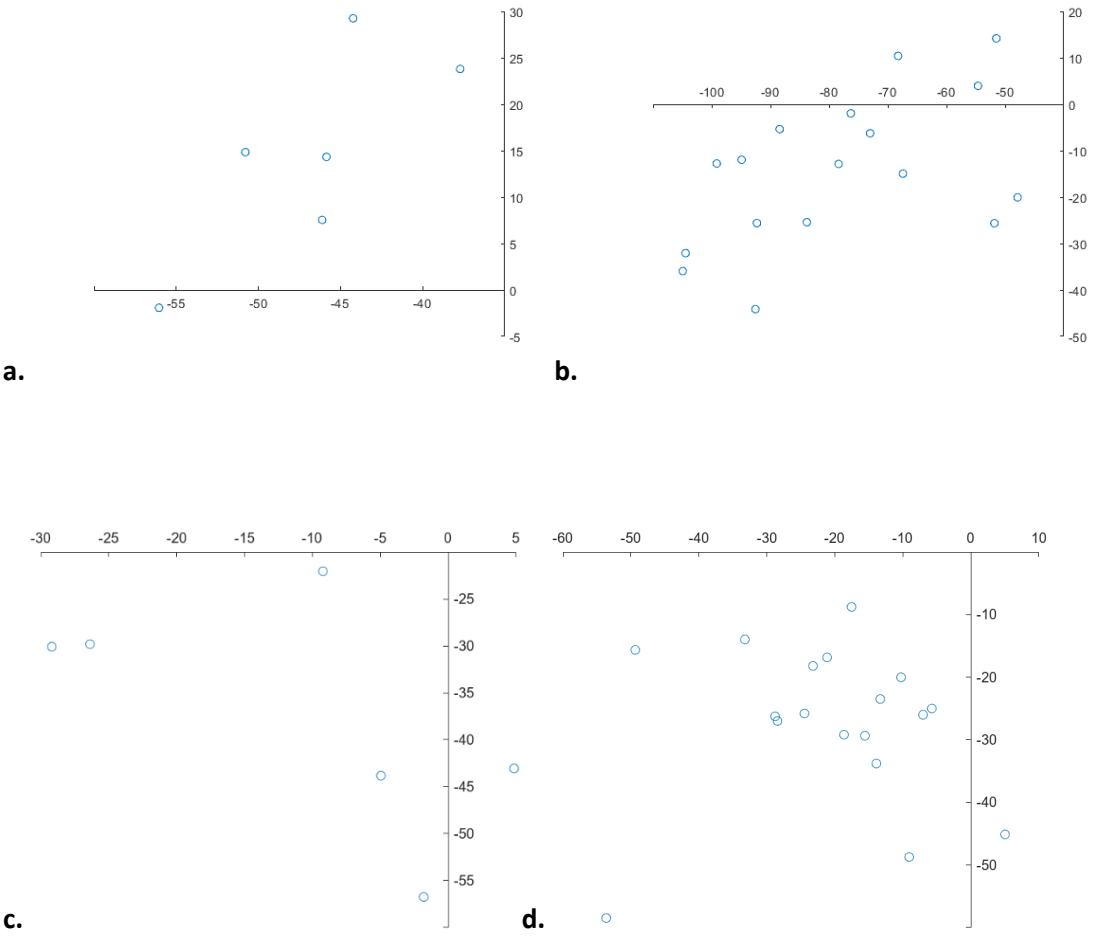
Participant	Group	WGS	WG
111	Non-clinical	23.74	24.52
112	Non-clinical	13.37	12.42
113	Non-clinical	14.74	18.98
114	Non-clinical	22.20	24.96
115	Non-clinical	14.74	12.84
116	Non-clinical	22.82	23.11
211	Clinical	13.68	15.97
212	Clinical	17.90	18.53
213	Clinical	29.36	32.53
214	Clinical	29.61	32.15
215	Clinical	10.35	14.66

Note. AVE units reported in mm.

Endpoint plots were generated for each participant, but only one participant from each group endpoint plot to a target in both conditions is reported (WGS/WG).

Figure 4

Endpoint plots for one clinical and one non-clinical participant



Note. Endpoint plots are from a non-clinical and a clinical participant who were age and gender matched. Endpoint plot a: clinical WGS; b: clinical WG; c: non-clinical WGS; d: non-clinical WG. Endpoint plots were generated in a MATLAB code therefore the scales are relative to each target results.

5.3.3 *Range of Motion*

5.3.3.1 Non-Parametric results.

A general pattern of no effect of startle was observed for all ROM. Mean ROM for all joints can be found in Table 8. Results of a Wilcoxon signed ranks test showed no significant effect of startle for all joints: wrist ROM (Z = -0.711, p = 0.477), elbow ROM (Z = -0.711, p = 0.477), shoulder ROM (Z = -1.334, p = 0.182), and thorax ROM (Z = -1.478, p = 0.139).

Table 8

Mean joint ROM for wrist, elbow, shoulder, thorax

	Wrist		Elbow		Shoulder		Thorax	
Participant	**WGS**	**WG**	**WGS**	**WG**	**WGS**	**WG**	**WGS**	**WG**
111	9	8	65	66	24	25	1	2
112	3	8	53	52	11	11	3	2
113	17	18	58	56	38	36	5	4
114	10	7	75	69	28	26	8	9
115	5	3	54	55	11	12	6	6
116	16	13	62	64	24	25	5	3
211	9	10	51	46	13	11	4	4
212	18	20	36	36	17	16	4	3
213	5	5	14	13	9	9	6	6
214	13	13	41	41	13	11	9	7
215	8	4	34	34	14	12		

Note. Mean joint ROM in degrees for wrist, elbow, shoulder, and thorax in WGS and WG conditions. All participants' ROM were calculated for each joint, except thorax. One participant was missing a thorax measurement due to the inability to place a thorax marker at the intended position of T8 which was covered by a wheelchair. All ROM measurements have been rounded up to the nearest integer.

5.3.4 *Joint Coordination*

5.3.4.1 Angle-Angle diagrams.

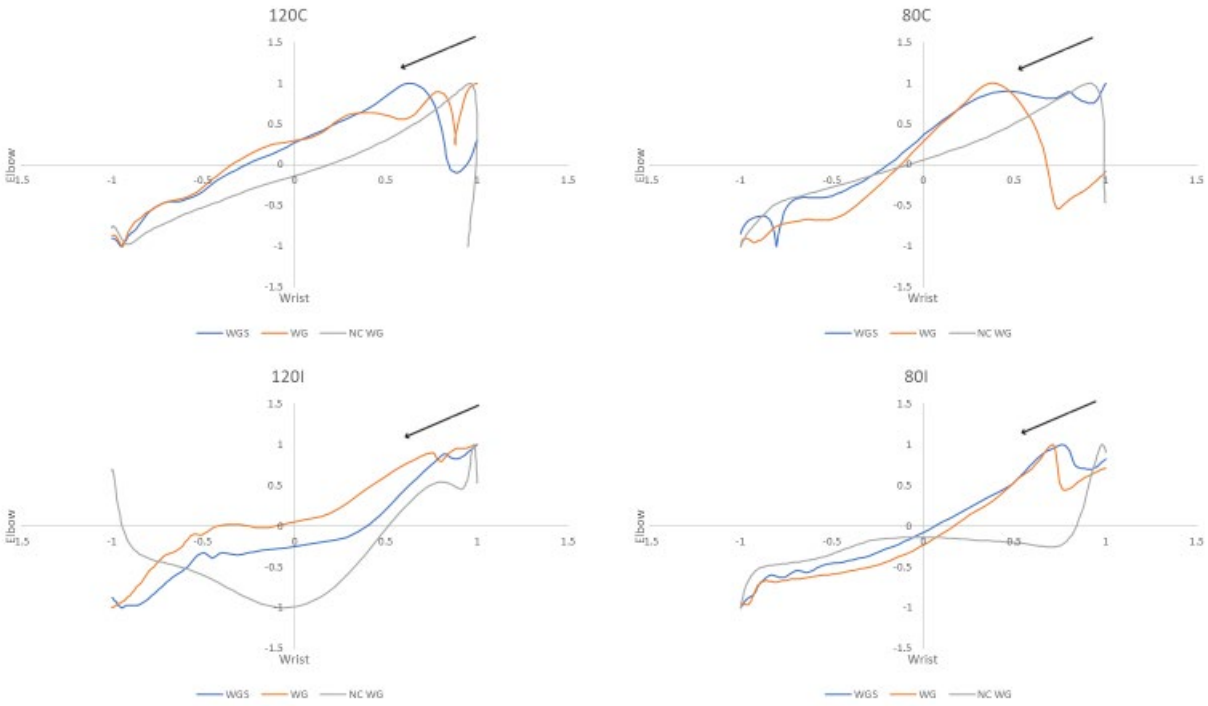
Figure 5 illustrates pattern of coordination between wrist and elbow during the reach for non-clinical and clinical groups and the effect of presenting the auditory startling stimulus, using time and

magnitude normalized flexion-extension angle-angle diagrams. In this figure, angle-angle diagrams for the clinical group in WG and WGS conditions are plotted against those from the WG conditions in the non-clinical group. As expected, coordination of the wrist-elbow during the reach in stroke survivors was altered compared to that of their non-clinical counterparts. For the current cohort, these differences could be qualitatively characterized by both altered trends and reversals, particularly at the end and beginning of the reach. Importantly, the startling stimulus affected this coordination within stroke survivors for different reaches to different targets.

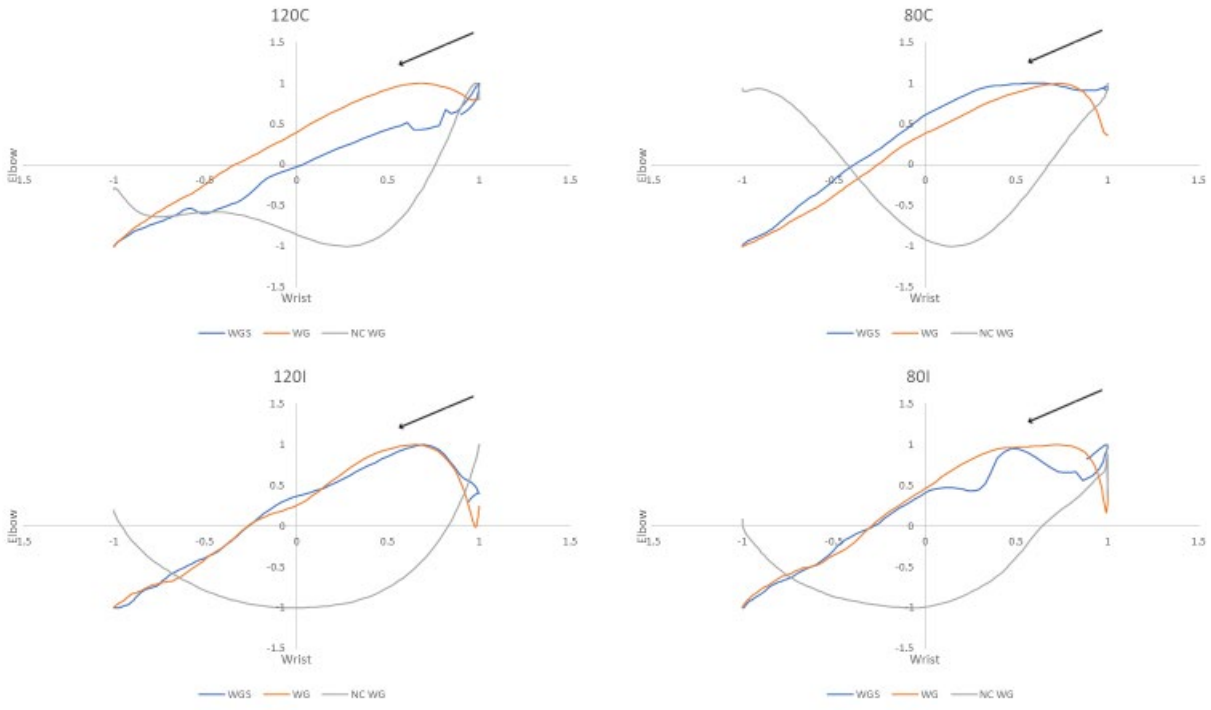
Figure 5

Angle-Angle diagram

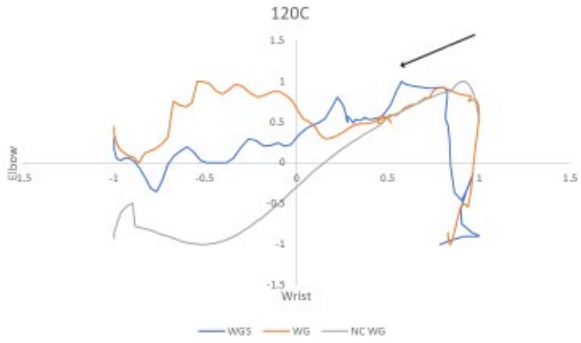
a)

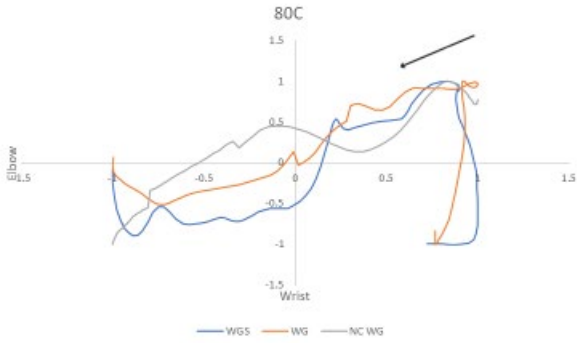


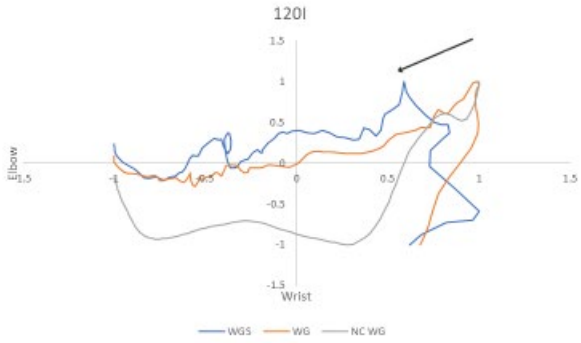
b)

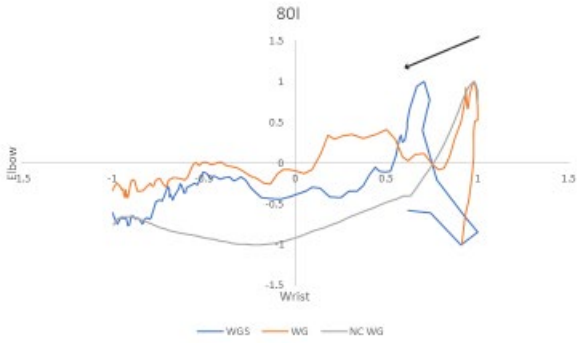


c)

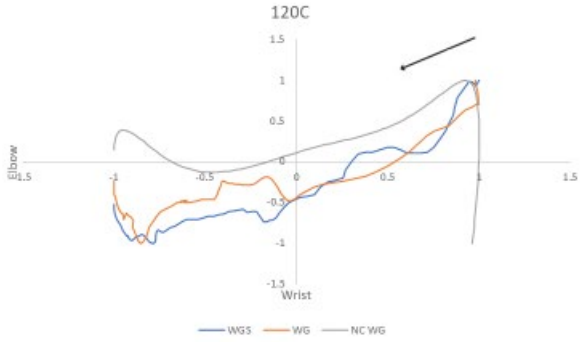

120C
Elbow
Wrist
WGS
WG
NC WG

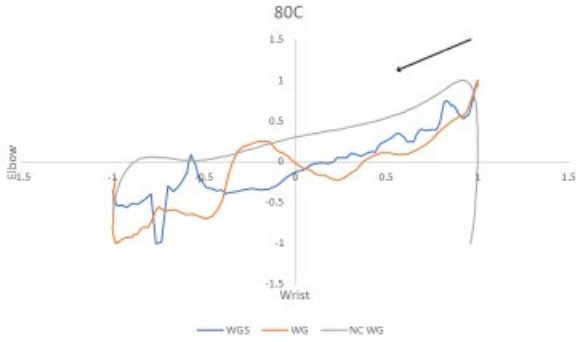

80C
Elbow
Wrist
WGS
WG
NC WG

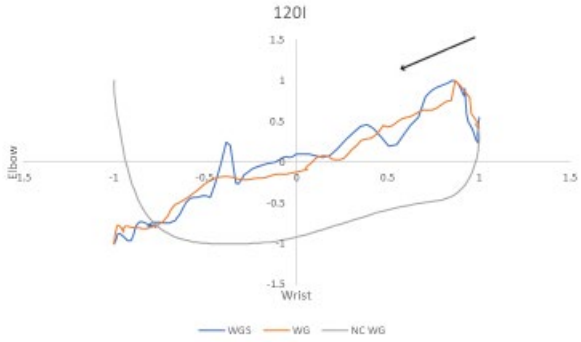

120I
Elbow
Wrist
WGS
WG
NC WG

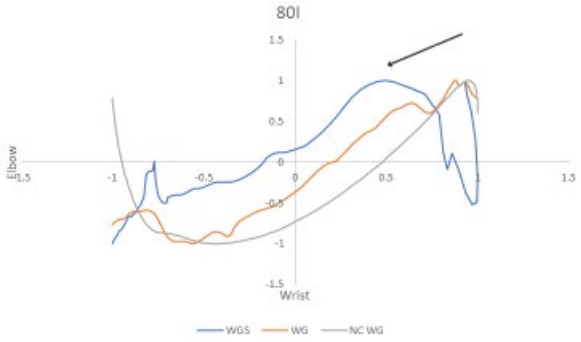

80I
Elbow
Wrist
WGS
WG
NC WG

d)

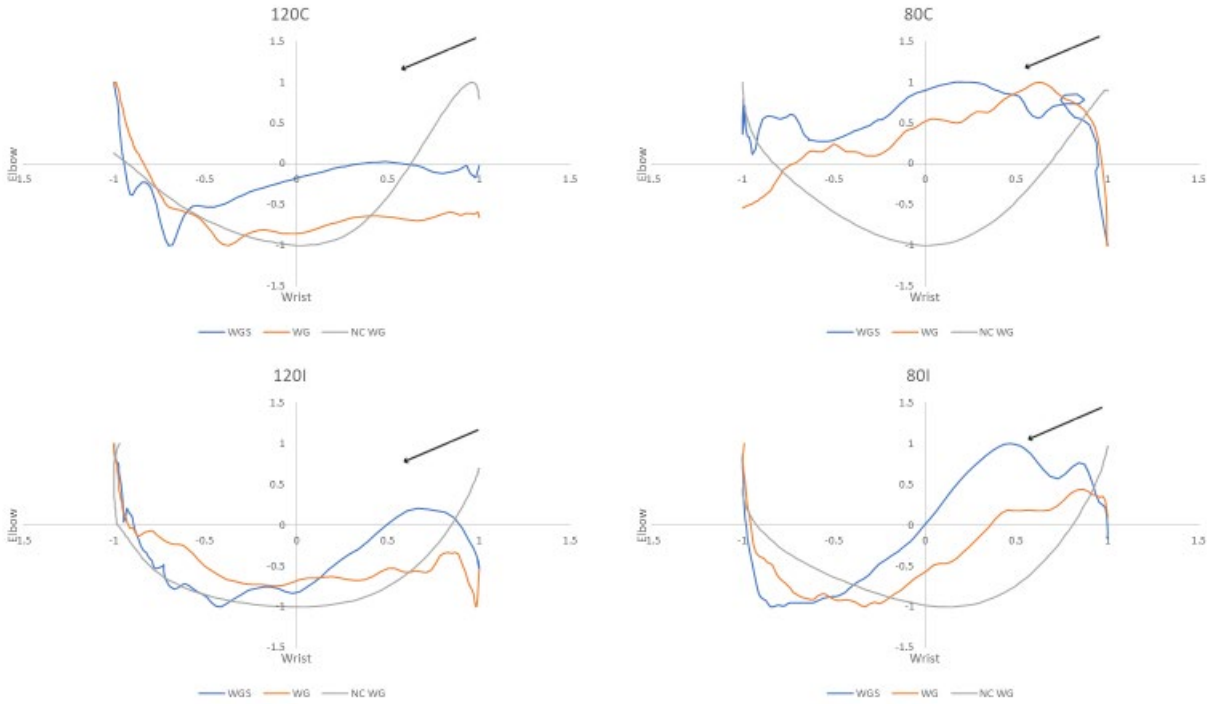

120C
Elbow
Wrist
WGS
WG
NC WG


80C
Elbow
Wrist
WGS
WG
NC WG


120I
Elbow
Wrist
WGS
WG
NC WG


80I
Elbow
Wrist
WGS
WG
NC WG

e)



Note. Time and magnitude normalized mean angle-angle diagrams showing flexion/extension coordination between the elbow and wrist for each clinical participant WGS and WG and age/gender matched non-clinical WG. Increasing numbers indicate flexion of wrist and elbow joint. Decreasing numbers indicate extension of wrist and elbow joint.

5.3.4.2 **CRP.**

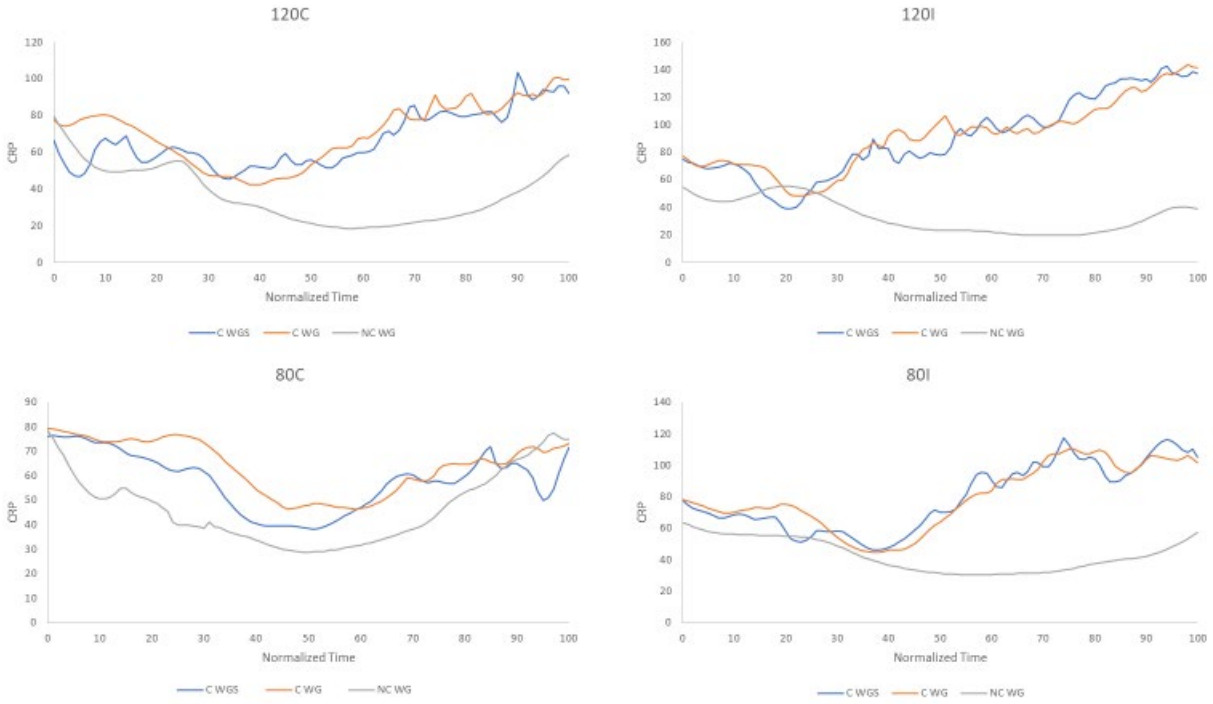
Differences in the time normalized CRP curves illustrated in Figure 6 were another representative of altered coordination pattern between the wrist and elbow joints, both between the groups and within the clinical group in the presence of a startle. In the non-clinical group, some general trends could be identified: for this group, the elbow joint initially lead the movement, but this pattern was reversed for most of the remaining part of the reach, with the wrist joint taking the lead and the two joints mainly moving in-phase. In the proximity of the target, in particular, the wrist joint took the lead. In contrast, pattern of coordination between the wrist and elbow joints in the clinical group did not show any identifiable common trend during the reach: the clinical WG and WGS CRP curves had multiple

peaks (reversal of the curves) representing lack of proper control and continual change in the leading joint. In other words, ongoing changes in the leading joint were depictive of upper limb impairment during the reach in stroke survivors. The general shape of the trajectories between WG and WGS CRP curves were more or less similar. However, fewer number of curve reversals in the non-clinical WG condition was suggestive of relatively more in-phase coordination between the two joints.

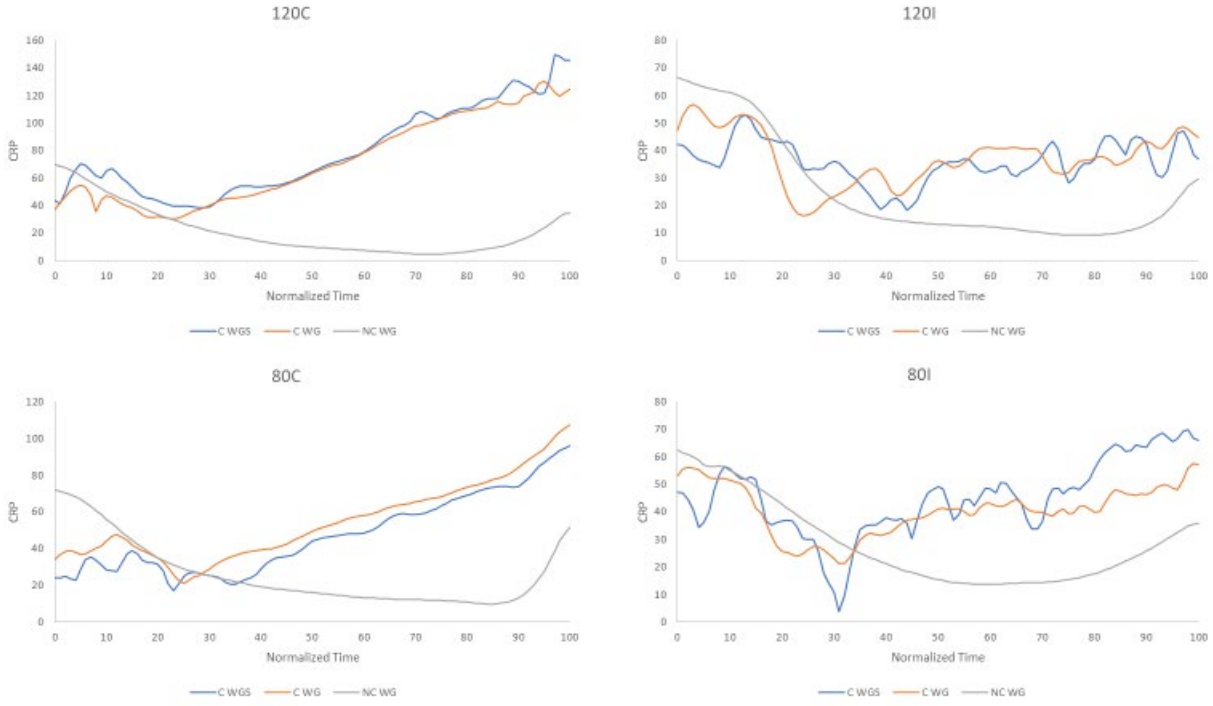
Figure 6

CRP graphs for the clinical and non-clinical groups

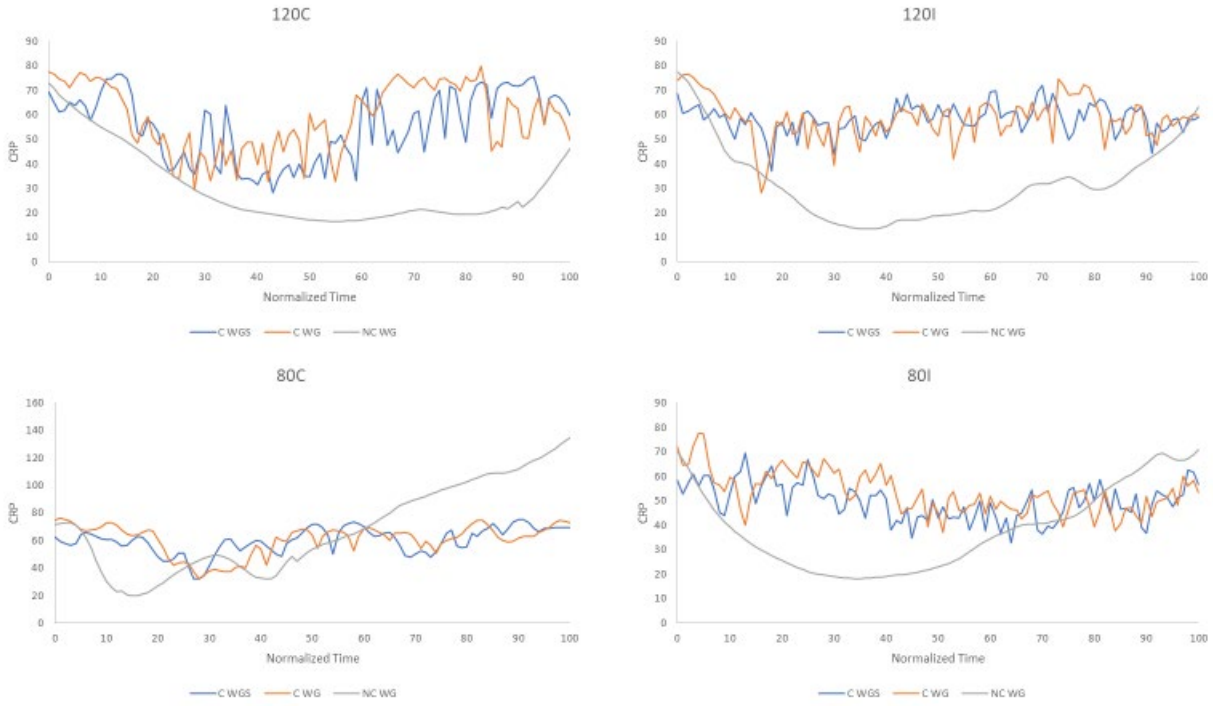
a)



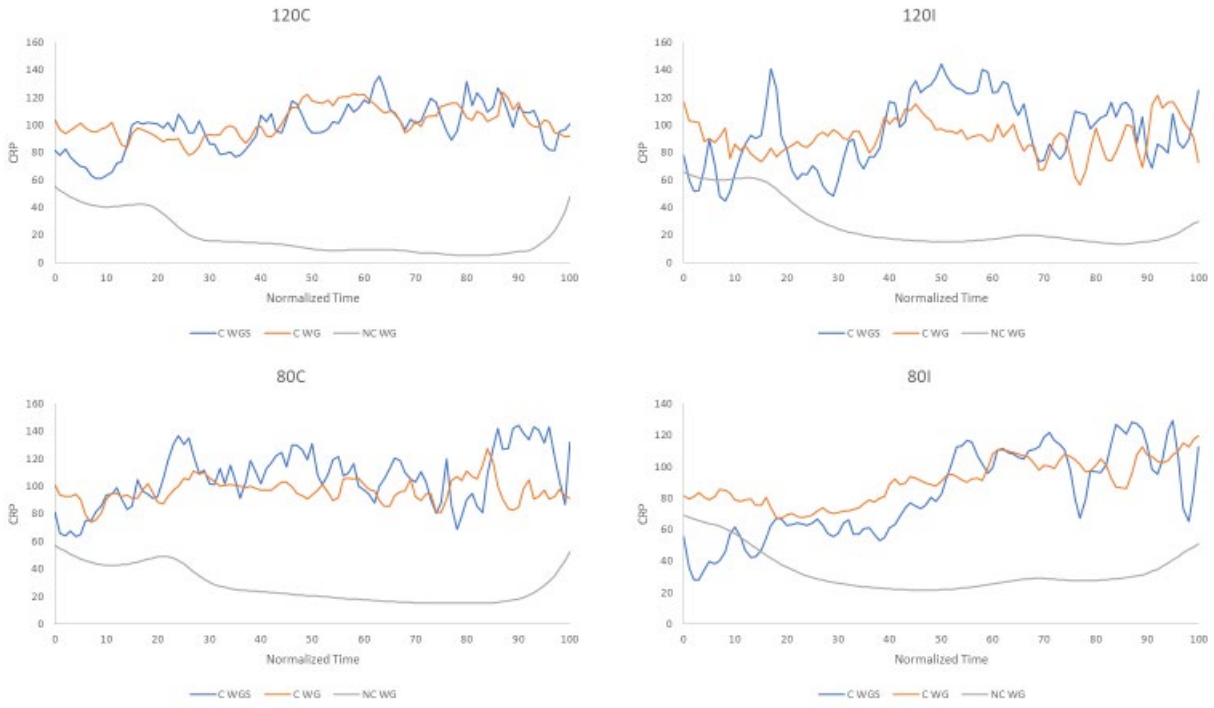
b)


120C
120I
80C
80I
CRP
Normalized Time
C WGS
C WG
NC WG

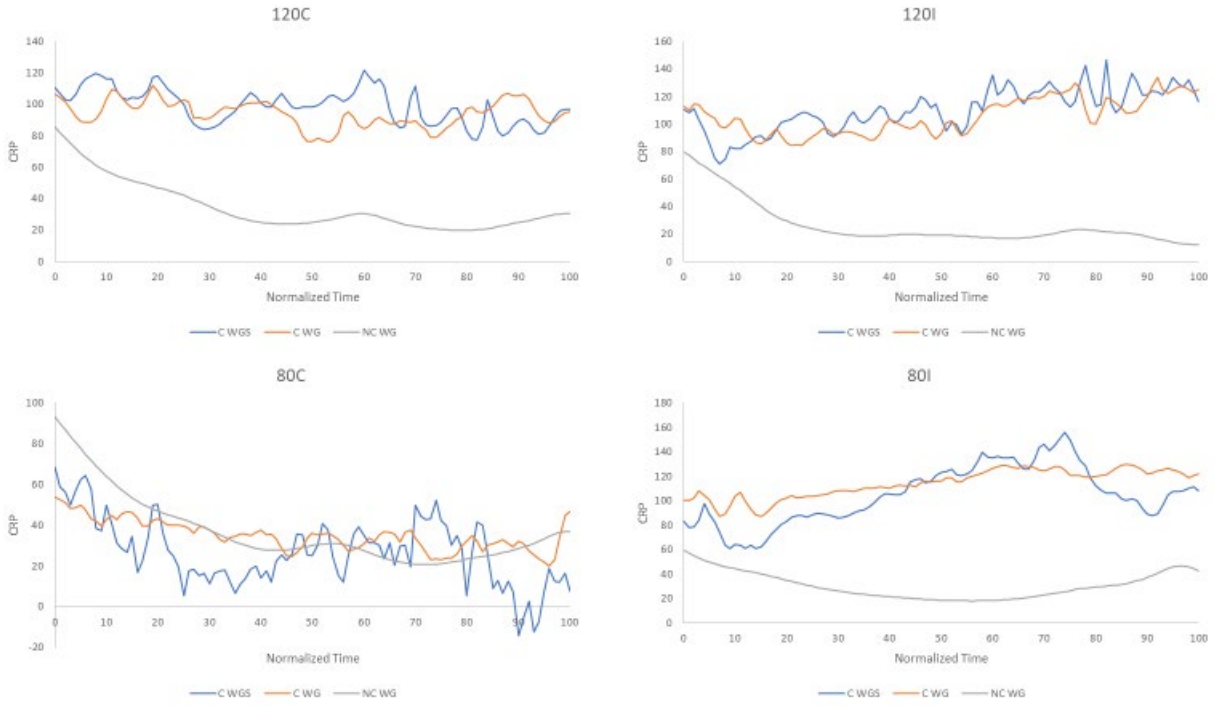
c)


120C
120I
80C
80I
CRP
Normalized Time
C WGS
C WG
NC WG

d)



e)

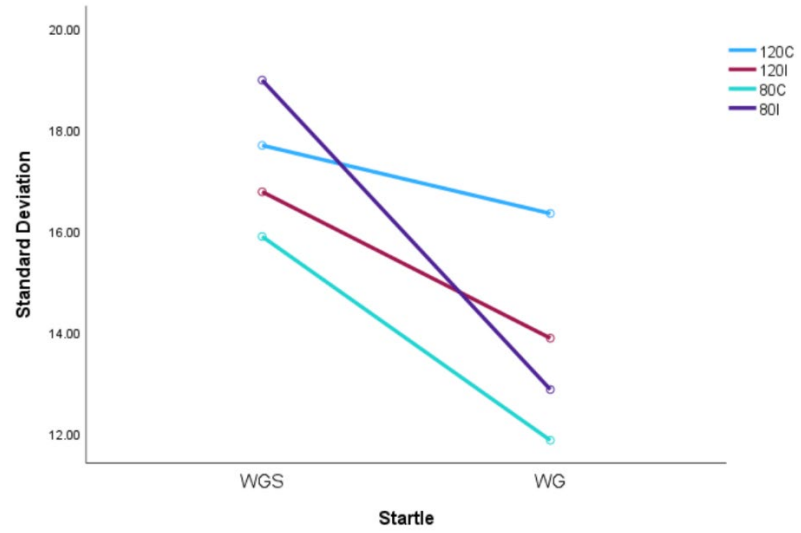


Note. Time normalized CRP elbow-wrist from onset to maximum reach. Each graph contains clinical WGS and WG and age/gender matched non-clinical WG.

The difference in clinical WGS and WG CRP curves was hard to visually assess further, and hence, standard deviation of the CRP curves was calculated to measure variations of the CRP values for each target (Figure 7). In the clinical group SD graph, all targets showed an increase in SD when a startle was involved. However, a Wilcoxon signed ranks test showed such increase was not statistically significant (Z = -1.826, p = 0.068). In the non-clinical group, SD of the CRP curves for different targets did not follow a consistent pattern, and not surprisingly, a Wilcoxon signed ranks test showed a nonsignificant result (Z = -0.730, p = 0.465).

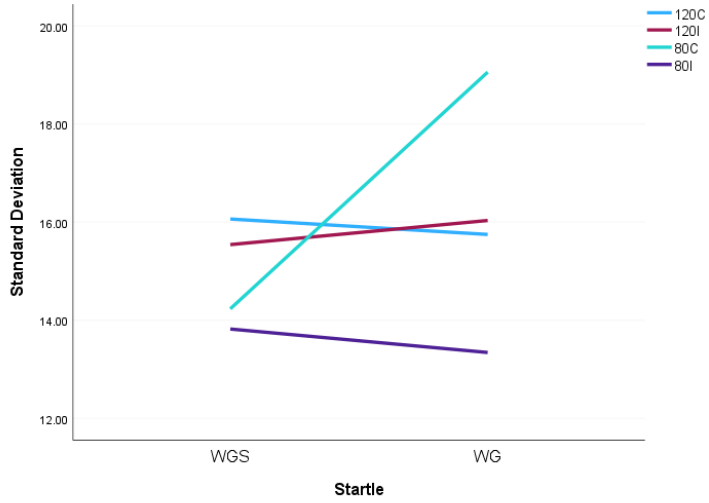
Figure 7

SD of CRP wrist-elbow



a.

b.



Note. SD from clinical (a) and non-clinical (b) CRP values of each target for WG and WGS conditions.

5.4 Discussion

The aim of the current study was to determine if kinematic and endpoint accuracy of an unconstrained goal-directed reaching task, performed in a StartReact experimental context, was altered in stroke survivors. The results showed PMT was faster, endpoint accuracy increased, and kinematic changes were suggestive of increased variability when the startle was presented in both groups.

5.4.1 *PMT and Movement Time*

A prepared (pre-programmed) reaching task was released faster in response to a startling auditory stimulus presented simultaneously with a visual imperative 'go' signal to move in stroke survivors. The results on PMT were consistent with Chapter 4, adding to the theory that StartReact phenomenon can be seen in chronic stroke survivors (Carlsen et al., 2012; Coppens et al., 2018; Honeycutt & Perreault, 2012; Lee et al., 2022). Previous investigations, including the study in Chapter 4, show that StartReact (presence of a startling stimulus) decreases the amount of time between the onset of the startling stimulus and onset of muscle activation in a simple reaction time task (Carlsen et al., 2012; Coppens et al., 2018; Honeycutt & Perreault, 2012; Lee et al., 2022). However, this is the first study which showed PMT decreased in an unconstrained goal-directed reaching task in stroke survivors, and that such effect of the startling stimulus on PMT was not different to those of an age- and sex-matched non-clinical control group. The results of this study were from a sample size of six in each group and lead investigators to the notion that this should be investigated in a larger population of stroke survivors.

A central theme in the StartReact literature is its application in studying the ability to plan and release preprogrammed movements (Castellote et al., 2007; Maslovat et al., 2011; Rahimi & Honeycutt, 2020; Valls-sole et al., 2008), with some authors reporting preservation of such ability in the stroke population, despite their limited ability to voluntarily accomplish the movement (Honeycutt & Perreault, 2012; Rahimi & Honeycutt, 2020). The ability to plan and voluntarily execute a movement involves

structures within the motor cortex, but when a startle is involved, the theory is that there is not enough time for cortical involvement (Valls-Sole et al., 1999). Therefore, Valls-sole (1999) suggests the voluntary movement plan (pre-planned movement) is triggered by the stimulus in the reticular formation and is carried out through the RetST resulting in the shortened PMT. The RetST is known to be involved in the startle reflex (Valls-Sole et al., 1999) and has input in voluntary motor control in primates (Baker, 2011).

In a population that consists of participants who have had a stroke and thus a range of motor impairments, it is likely that the motor cortices and their more direct connection with the spinal cord (e.g., via corticospinal tract) are damaged in some way. The stroke participants' ability to then plan and initiate the movement faster in response to a startling stimulus suggests plasticity or involvement of other motor pathways (e.g., reticulospinal tract) being responsible for the observed facilitation in the release of the response (Honeycutt & Perreault, 2012). The results from this study show there is a potential for shortening of PMT in an unconstrained reaching task and could add to the theory that stroke survivors can pre-plan an appropriate movement and use alternate motor fibers in the early release of the prepared movement, but require further research.

5.4.2 *Coordination Pattern*

Coordination pattern of a reaching task executed by stroke survivors in a StartReact experimental context altered in response to the presence of the startling stimulus. Although PMT was significantly shortened when the startling stimulus was involved, there was no significant effect of startling stimulus on movement time. This is in line with previous studies that have shown no effect on movement time from the stimulus (Carlsen et al., 2004; Maslovat et al., 2011). Even with a significantly faster PMT, the overall time for completion of the movement remained the same. After a stroke, movement times in a goal-directed task are expected to be slower when compared to non-clinical individuals due to motor impairment (Bourke, 2015; Levin, 1996). As stated in the results before, all

reaching movement times were pooled together regardless of target location. As a result of having an ID of 2, movement times did not change at different targets allowing for the pooling together of data. Movement times at each target are presented in table 6.

A previous study performed on temporally and spatially defined movements used a predetermined movement time (temporal) and an untimed task (spatial) to compare and explain kinematics and muscle activation patterns in StartReact conditions. Temporal target conditions were a reach to a specified target in a predetermined amount of time, and the spatial conditions were reaches to the predetermined targets with no time constraint (Maslovat et al., 2011). In both trial types, movement time was not directly affected by the startling stimulus. Maslovat et al. (2011) suggested that the lack of effect seen was due to participants' movements slowing after the initial effects from the stimulus that started the movement faster. Data from the current study showed a similar trend to Maslovat et al. (2011), although only the untimed (spatial) task from this study is relevant to the present investigation. In the present study, movement times did not change between the startling conditions, and Fitts' Law prevailed. Please note that the purpose of the current study was not to examine the effect of StartReact on movement time, and a task ID was employed which would not discourage participants from attempting the task by a possible mismatch between participants' perception of their physical abilities and task requirement. Therefore, emphasis is put on the fact that participants in this study performed the task according to expectations as could be manifested by the PMT and movement time results, and hence any altered coordination pattern between the two stimulus conditions could be attributed to the potential effect of the startling stimulus rather than characteristics of the cohort (below).

Previous work which examined movement kinematic in StartReact experimental context involved single joint tasks (primarily flexion/extension of the wrist) (Ossanna et al., 2018). Recently,

some studies have progressed to multi joint tasks(Ossanna et al., 2018). Investigations such as those by Carlsen et al. (2004), looked into the kinematic of a multi joint movement task with outcome measures that consisted of PMT, displacement RT, angular displacement and velocity, and movement time. Authors found no significant change in the kinematic between startle and control trials. The kinematic measured was in 2D and of constrained movements which used a manipulandum. Position measurements taken in Honeycutt and Perreault (2012, 2014) had similar characteristics. 3D motion analysis gives the added benefit of freedom of inter-joint coordination with no confounding effect from constraints imposed by interacting with an object/device.

The current results reported two forms of joint coordination measures. One was an angle-angle diagram, and the other was continuous relative phase, both representing the inter-joint relationship of the wrist-elbow. Two measures of coordination were chosen because they individually measured different characteristics of joint coordination. CRP is a temporal measure that describes the change in phase angles of the two joints throughout the movement and angle-angle diagrams define the spatial relationship demonstrated by the two joints throughout the movement (Tomita et al. 2017). In both coordination measures the non-clinical measurement was a predominantly smooth line and the clinical measurements had multiple peaks in the line meaning either a reversal of the df or a reversal of the leading joint. The differences in clinical and non-clinical coordination were to be expected, however the differences seen in the WGS and WG conditions of the clinical group was a matter to be further explored because of its theoretical and practical importance.

Previous literature, which discussed the kinematic of movements seen in StartReact, reported that movement kinematic did not change when a startling stimulus was present (Carlsen, 2004; MacKinnon et al., 2013). The measurements used to reach these conclusions were often 2D measurements and did not have a measure in joint coordination. To measure the relationship between

two joints and descriptively analyze coordination patterns, angle-angle diagrams are often used. Figure 5 shows such coordination patterns for the wrist and elbow under different stimulus conditions for the clinical group against that of WG condition for the non-clinical group which was used as the standard reach. Inter-individual differences in the non-clinical group were present as could be expected because the task was unconstrained and discrete. In the clinical group, under both WGS and WG conditions, the two joints extended for the majority of the reach. Compared to the non-clinical group, however, the clinical WGS and WG showed differences represented by the reversals of movement and altered slopes, mainly in the beginning and end of the reach suggesting initiation of the movement and its termination at the target were particularly problematic. Overall, the angle-angle diagrams were suggestive of altered inter-joint coordination when a startling stimulus was presented, as could be judged by the shapes of respective graphs in the two conditions.

To further investigate coordination, CRP is calculated. The CRP graphs were less clear when visually assessing for the presence of any kinematic changes. CRP graphs are not a regular tool used in clinical upper limb kinematic measurements (Daunoraviciene et al., 2017), and the present data can therefore provide additional insight into the potential usefulness of such an approach for future research. Some authors have used SD in CRP to represent the amount of variability seen in the movement (Daunoraviciene et al., 2017). Variability can be an indicator of changes in movement patterns. It can represent instability or represent the appearance of a new movement pattern (Daunoraviciene et al., 2017). Previous studies have reported an increase in variability in movements influenced by a startling stimulus (Carlsen 2004; Ossanna et al., 2019). To analyze the differences seen in the CRP graphs when a startling stimulus was present, SD of the CRP for each target was considered in the WGS and WG conditions of both groups. Figure 7 shows the SD of the curves in both WGS and WG conditions. There was a consistent but statistically non-significant increase in SD in the WGS condition for all target locations of the clinical group. This suggested an increase in the variation seen around the

mean of CRP values, and further suggests the possibility of altering coordination patterns by presenting a startling stimulus to the clinical group.

It can be theorized that use of alternate motor fibers in StartReact contexts may not be limited to the early release of a preprogrammed movement, but provides the opportunity to expand motor repertoire of the participant by supporting a wider set of motor units than those which are regularly activated through the remaining corticospinal pathway. This theory was established from a small sample size and should be further studied to determine if similar trends are seen in a larger sample size. The functional benefit of such alteration can be examined by looking into the alteration in the accuracy of completed movement.

5.4.3 *Endpoint accuracy*

A reaching task initiated in response to a startling auditory stimulus was executed more accurately than a reaching task with no startling stimulus. Using AVE, variability in reaching endpoints was measured about their own mean as a measure of reaching accuracy between startle and control trials in both groups. A significant decrease was found in endpoint variability when a startle was involved. A previous study that investigated final error in StartReact found no improvement in final error (Rahimi et al., 2020). Authors used the lack of change in final error to argue startle movements were possibly not functional. However, the results of the current study showed a decrease in endpoint variability in startle trials. This shows a potential for the reach to be more accurate when a startling stimulus is presented creating a more functional movement. Endpoint plots showing participants accuracy can be seen in Figure 4. It is important to note the change in variability can be a statistical artefact due to the difference in number of trials between the startle and non-startling conditions or due to compensatory trunk flexion.

In the chronic phase of stroke, a predominant theory in rehabilitation for improving functional abilities is that changes seen in movements are mainly from compensation for the lost motor control. An example of such movements is producing more trunk flexion when reaching which can compensate for the limitation of movement at the elbow and shoulder joints (Hammerbeck et al., 2017). The reach may seem farther or more accurate, but the movement in the upper limb is not improving or becoming more functional due to the increased trunk flexion compensating for the lack of upper limb extension. In Cirstea and Levin (2000) participants performed a reaching task and 3D analysis of the movement was performed. Authors suggested the increased trunk movement was due to the increased impairment of the arm performing the reach. Authors found a direct correlation between trunk engagement and limited arm degrees of freedom. This study did not limit participants' trunk movement. This allowed for the ability to determine if any changes seen in the startle trials were due to compensatory movements or changes in upper limb kinematics. A statistical analysis of thorax ROM in startle trials showed there was no significant effect when a startling stimulus was present. Two things can be concluded from the thorax ROM: 1) The decrease in endpoint variability was not due to a compensatory trunk flexion; 2) Kinematic changes seen in the movement were likely to be due to changes in the upper limb kinematic not trunk flexion.

5.4.4 *Movement Variability*

A common concept from motor control theories including uncontrolled manifold, general motor program and dynamical systems theory is that a movement with a decreased amount of variability is a stable movement (Stergiou & Decker, 2011). Using this concept, it can be perceived that an impaired movement, after stroke, has a decreased amount of variability resulting in the loss of ability to adapt in interaction with environment and requirements of the task. Conversely, variability is seen as a sign of a healthy system and gives the movement the ability to adapt and be more flexible (Hamill et al., 1999).

The theory of optimal movement variability has been proposed by Stergiou et al. (2006). This theory builds mostly from dynamical systems theory and suggests that each movement has an optimal amount of variability and any deviations from this whether increased or decreased induce complications in the movement (Harbourne & Stergiou, 2009; Stergiou et al., 2006; Stergiou & Decker, 2011). Following this theory an increase in variability in a rigid or stable system (decreased variability), such as in a hemiparetic system, could make the variability reach an optimal state and create a more functional movement pattern.

After a stroke, movement of the upper limb is often described as having slower movements, decreased ROM, and an increase in variability (Cirstea & Levin, 2000; Ranganathan et al., 2019). However, the variability used in the description should clearly state what type of variability is being used. Often, if there is an increase in variability, the increase is in SD of kinematic measures such as peak velocity, peak displacement, movement trajectory and movement time (Cirstea & Levin, 2000; Sethi et al., 2013). This increase in variability can be used to describe the outcome of the movement that occurs, but it does not describe the coordination that led to the movement (Sethi et al., 2013; Tomita et al., 2017). Movements after a stroke are also often described as rigid, inflexible, and stable demonstrating a decreased amount of variability (Harbourne & Stergiou, 2009; Stergiou et al., 2006). The inconsistency in the literature can be attributed to the measurement of variability that is used (Stergiou et al., 2006). Theories such as dynamical systems theory predict that changes in movement patterns from an initial (stable) movement pattern/state to another state is preceded by a period of an increased amount of variability which is the prerequisite for pushing the system out of a particular phase state (Daunoraviciene et al., 2017; Stergiou et al., 2006). Subsequently, if the rigid and inflexible coordination patterns after stroke could be conceived as a stable state, and the purpose of rehabilitation as inducing more variability into the motor control system with the purpose of expanding motor repertoire, then theoretically any attempt to increase segment or joint variability during functional task may lead to

improving function by supporting motor synergies (e.g. via error compensation) during execution of a task and using sensory feedback to support neuroplasticity at higher levels.

In the current results of the clinical group, trials with a startling stimulus had an increased chance of altering participants' movement patterns due to the increase in coordination variability as could be understood from the altered CRP. In other words, the increased coordination variability seen in the movements with a startling stimulus could be giving the system more options to consistently complete the movement and improved endpoint accuracy. The results showing an increase in movement variability in the pattern of coordination between the wrist and elbow points to the theory that StartReact has the potential to be exploited as a rehabilitation tool. Future investigations should first look to measure variability in a large stroke population and, if the results are in line with what is seen in the current study, look at the possibility of developing training protocols which involve alternate motor fibers (e.g., reticulospinal tract) with the view of assessing their long-term effect on improving function and using nonlinear tools as suggested by Harbourne and Stergiou (2009) to evaluate the coordinative variability seen in the impaired systems.

5.5 Limitations

A pragmatic approach to recruitment was used and this study did not have a measure of impairment levels in the clinical group. Future studies would benefit from knowing the impairment levels of each participant so results on kinematic changes can further be subdivided into levels of impairment. This would give an insight into if StartReact is more robust in some levels of impairment than others, and hence any approach to rehabilitation using StartReact may be more suitable to a particular group. As in Chapter 4 when analyzing the results, all PMTs recorded were included with no upper or lower limit. Not having an upper limit of PMT includes trials where the participant was potentially inattentive to the task. Having an upper limit might decrease the overall means of the PMT.

EMG was only on an agonist muscle of the reach. Future studies would benefit from also having EMG of the antagonist muscle to compare muscle activation patterns of the reach. As in Chapter 4, the sample size of this study was low and all results reported should be considered as exploratory and used as a platform to build future research.

5.6 Conclusion

The aim of the current investigation was to determine if the presence of a startling stimulus could induce kinematic alterations and improve endpoint accuracy in a reaching task completed by stroke survivors. The cohort in the current study had an improved endpoint accuracy, shortened premotor time, and inter-joint coordination changes when a startling stimulus was involved. The findings are suggestive of the notion that the effect of StartReact may not be limited to the preparation stage of movement (by shortening of the PMT or reaction time) and execution phase of movement can also be affected, and therefore, could be exploited into a tool for stroke rehabilitation.

The results only give a preliminary idea of the capabilities of StartReact as a potential rehabilitation tool, and future studies could take a dynamical systems (theoretical) approach to studying StartReact and quantifying the associated movement variability. The use of nonlinear tools could provide a more comprehensive investigation into the coordination variability. The results reported are limited due to the small sample size and conclusions should be interpreted as a basis for further investigation.

Chapter VI General Discussion

6.1 Summary of Main Findings

In clinical populations where the CST is compromised, there is potential for other descending pathways, generally known as AMF to compensate for the loss. In the present doctoral thesis, the overall aim was to evaluate the feasibility of using AMF in stroke rehabilitation. This was accomplished by examining the use of a startling stimulus, emitted at the same time as a 'go' cue while the participant was prepared to move, on movement preparation and execution in stroke survivors. The experimental context is known as StartReact (Alibiglou & Mackinnon, 2012; Carlsen et al., 2012; Castellote et al., 2017), and is suggested to prompt RetST involvement in executing a movement.

StartReact ability to employ RetST has been used in clinical populations with motor impairment such as stroke (Castellote et al., 2017; Rahimi & Honeycutt, 2020), Parkinson's Disease (Nonnekes et al., 2015), hereditary spastic paraplegia (Nonnekes et al., 2014) and spinal cord injury (Baker & Perez, 2017) to influence voluntary movement. The RetST is currently the most promising alternate pathway to influence movement due to its parallel descent near the CST and its projections in the spinal cord being close to the projections of the CST (Lemon, 2008). As mentioned in the literature review chapter, the termination points of the RetST are similar to the termination points of the CST, but they are not specific enough to have control over fine motor skills (Baker, 2011). The RetST is known to have control over locomotion, posture, reaching, proximal and distal control of limbs (Baker et al., 2015; Lemon, 2008; Lemon et al., 2012, Riddle et al., 2009). Most of what is known about the RetST is from animal studies and studying StartReact phenomenon (Honeycutt et al. 2013; Lawrence & Kuypers, 1968; Riddle et al. 2009). The potential for the RetST to be spared following damage to the CST and the known control the RetST over some movements has created the notion of exploiting it as a potential means for rehabilitation after damage to the CST in stroke survivors.

The first study in Chapter 3 sought to validate the use of StartReact in the stroke population through a systematic review and meta-analysis. The literature was systematically searched for all studies that utilized a StartReact protocol with a stroke population. There was a scarce number of studies found in the literature, but from the studies included it could be established that StartReact was intact in the chronic stroke population. Results showed a decrease in PMT in both clinical and non-clinical groups when a startling stimulus was present. The difference in PMT in the clinical group in the presence of startling stimulus was a decrease of 86.72 ms and in the non-clinical group was a decrease of 42.22 ms. In Chapter 3, the results were written using the term RT instead of PMT. This was noted in the methods due to the interchangeable use of the word in the literature in StartReact context, but the rest of the thesis referred to the PMT when the effect of startling stimulus on the onset of muscle activity was an outcome measure and this approach remained faithful to the classical motor control literature. Importantly, this review found there was not a widely agreed upon protocol for StartReact, specifically relating to the intensity (dB) level of the sound and that a measure of startle should be included (e.g., activity in the SCM muscle).

The second (experimental) study in Chapter 4 was built on the findings that StartReact was intact in stroke survivors and addressed an area of protocol for being used in stroke participants. PPI and PPF are known manipulations of the startle reflex through varying the relative timing of the 'warning' and 'go' cues (Aasen et al. 2005; Maslovat et al., 2012). This chapter aimed to determine if the time between the 'warning' cue and the 'go' cue (ISI) had any effect on PMT. StartReact stems from the startle reflex literature. The effect the ISI has on PMT has been investigated in startle reflex literature with clinical and non-clinical participants, but not in the stroke population. Therefore, it was not clear whether ISI would have similar effect on StartReact in this group. This study employed a button-press task and multiple trials with a 'warning' and 'go' cue (with or without startling stimulus) were presented. The ISI between the two cues varied between 50 and 2400 ms, which was expected to produce a PPI or

PPF according to published literature (Aasen et al. 2005; Maslovat et al., 2012). Results from Chapter 4 were from a small sample size and need to be corroborated in a larger stroke population, but tentatively showed PMT was faster when a startling stimulus was present, and the range of ISI employed did not affect the PMT in either clinical or non-clinical groups. This showed there was not a specific ISI between 50 and 2400 ms that would inhibit or facilitate PMT in stroke survivors. Subsequently, this information was used to create the protocol for study 3.

The third (experimental) study presented in Chapter 5 combined the knowledge from the first two studies and aimed to determine if there were changes in movement kinematic or endpoint accuracy during a StartReact reaching task in stroke survivors. The reaching task used was an unconstrained discrete goal directed reaching task. Participants had one out of four targets to reach, which had the same low index of difficulty (ID=2), in a StartReact context. The low ID employed was subject-specific and determined based on each individual's limit of workspace. This encouraged stroke participants to execute the movement. Results were in line with the previous two studies showing PMT was faster when a startling stimulus was present while movement time followed Fitts' Law and did not change with alteration in movement amplitude and target diameter for the fixed ID employed. Importantly, endpoint accuracy improved, and this was not believed to be associated with any changes in thorax movement, while the atypical inter-joint coordination between the wrist and elbow observed in stroke participants was affected when a startling stimulus was present. This was quantified by an increase in the standard deviation of wrist-elbow continuous relative phase (CRP) in the clinical group and suggested increased inter-joint variability in StartReact trials.

6.2 Use of SCM as a measure of startle may not be required

In classical startle reflex literature, there are two methods of measuring the presence of a startle response. Both methods utilize muscle activity seen when the startling stimulus occurs. One measure

uses activity in the SCM, and the other measure uses activity in the OOC as the sign of true startle (Carlsen et al. 2007; Valls-Sole et al., 1995). More recent studies in startle reflex and StartReact illustrate a shift towards a preference to use the SCM as a measure of startle (Leow et al., 2018; Smith et al., 2019). The shift to using SCM derived from the OOC muscle picking up the auditory blink response when there is not a startle involved (Carlsen et al., 2007). Furthermore, the SCM was one of the last muscles to habituate with the startle reflex (Carlsen et al. 2007).

Investigations that use SCM as an indicator of startle use this as a method of distinguishing the effects seen from the stimulus intensity (Carlsen et al., 2007). Accordingly, studies separated their results into results that have SCM activity (SCM+) and those that do not have SCM activity (SCM-) (Carlsen et al., 2007; Honeycutt & Perreault, 2012; Honeycutt et al., 2015; Coppens et al., 2018; Lee et al., 2022; Rahimi & Honeycutt, 2020). Results of these studies showed shorter startle PMT in SCM+ than SCM- trials.

Papers which used this method of identifying true startle trials based on activity in the SCM, often refer to Carlsen et al., (2007) in which authors aimed to determine if the faster PMT seen in SCM+ trials were caused by the startle or were simply due the increased stimulus intensity. Using a task involving wrist extension to a fixed target, Carlsen et al. (2007) performed multiple trials with startling stimuli at varying intensities (93, 103, 113, and 123 dB). 83 dB is the regular level of noise intensity and was used as the control noise level in this study. PMT in different trials were separated based on the presence of activity in SCM or OCC, or absence of any (muscle) response indicator (MRI). A main effect for intensity level and an interaction effect between startle indicator and intensity level were reported. There was no further analysis for the main effect of intensity level, however trend of data suggests startling stimulus intensity of 93 dB and above might have been all associated with reduced PMT, which questions the reported stimulus intensity effect on startle. Post hoc analysis of the interaction effect

showed SCM+ trials were faster than the other trials. An alternative explanation for the observed data could be that high (>=93 dB) auditory stimulus intensities simply induced a startle regardless of the presence of muscle activity in SCM or OCC, and SCM+ trials belonged to one end of PMT distribution spectrum, which according to the data illustrated in Figure 1 by Carlsen et al., (2007) was quite wide. Conclusions made by Carlsen et al. (2007) was considered a misinterpretation of their findings and that SCM activity at higher levels of noise intensity did not indicate the effect of stimulus intensity on PMT, or that SCM activity was required to represent true startle. Subsequently, the approach that noise intensities at >=93 dB would be associated with startle responses, regardless of presence of any EMG indicator from SCM or OOC was used.

Maslovat et al., (2023) further explored the area of using SCM as an indicator of startle and proposed the hypothesis that the difference in PMT between the trials with or without SCM (SCM+ or SCM-) activity measured the amount RetST involvement. Authors used StartReact in tasks involving the distal (finger) or proximal (shoulder) portions of the arm as the RetST influences the proximal part of the limb more than the distal. Authors found a greater reduction in PMT in the shoulder movements than the finger movements in startle trials. Authors proposed this as more evidence that the RetST has differing control over movements and trials with no SCM activity were not lacking in RetST involvement but had a decreased amount of involvement. The above interpretation of Carlsen et al., (2007) results, is compliant with Maslovat et al., (2023) proposal. Accordingly, this thesis takes the methodological position that any PMT recorded at stimulus intensities >=93 dB would be considered as startle trials, and with increasing stimulus intensity, trials with SCM activity would be more frequent that could be due to an increased level of RetST activation. In both experimental studies PMT were not separated between trials with SCM activity and without it due to this theoretical perspective.

6.3 Implications of StartReact for Stroke rehabilitation

The results from this thesis have some implications for StartReact literature. The main implication is providing preliminary data for future research to build upon. The results further the current theory that StartReact is available in chronic stroke survivors. Not only is the number of studies utilizing StartReact low, but the number of participants is also low. The experimental studies provided in this thesis add two more studies to the list investigating StartReact in stroke survivors, but also follow in the trend of low sample size. This highlights the need for a future project to complete an investigation in a larger population, while taking into consideration the current methodology discrepancies.

The results also show that PMT is significantly shortened when a startling stimulus is presented with the 'go' cue. While this is repeatedly shown in the literature; this study builds from the published literature and is the first study to show PMT has the potential to be shortened during an unconstrained goal directed reaching task. Importantly, the positive outcomes support StartReact potential benefit for stroke rehabilitation. Such potential could be attributed to the observed change in joint coordination patterns and improve endpoint accuracy in StartReact trials but needs further data collection to determine if this trend will be found in a larger sample size. This is a novel finding and might expand current knowledge on the effect of StartReact if it can be replicated in a larger study. Current practices view StartReact as a potential method to quicken movements but one which has no effect on overall movement patterns. The results provide basic findings to show that StartReact has the potential for changing the movement pattern at the joint level by increasing variability of inter-joint coordination. This has importance specifically in the clinical population where movement patterns are rigid and inflexible due to upper limb impairment. Impaired movement patterns and the effect of StartReact on them were examined in the Chapter 5 discussion.

The results showed a change in joint coordination in the two startle conditions, and following along the theory of optimal movement variability, the increased coordination variability between the

wrist and elbow joints could lead to a change in a more functional movement patterns with longer term training. Furthermore, the results showed a decrease in endpoint variability which indicated an increase in endpoint accuracy. Improvement in endpoint accuracy in a larger sample of the stroke population could indicate StartReact not only elicits a quicker pre-programmed movement, but a more accurate one. The finding of a decreased endpoint variability in the small sample of Chapter 5 can guide future investigations. Improved endpoint accuracy would be important in a rehabilitation protocol to promote functional movements. Importantly, the results showed the increase in endpoint accuracy was not due to an increase in trunk flexion as a compensatory strategy as previous studies suggest. This was demonstrated by thorax ROM not being different when a startling stimulus was present. It was speculated that improved endpoint accuracy came from the increased inter-joint coordination variability, which allowed more flexibility in the synergies formed between the joints for achieving the goal.

Collectively, this thesis makes the argument for the potential of AMF specifically RetST, to be used in stroke rehabilitation. A method of utilizing the RetST in rehabilitation could be following a StartReact protocol of training, but more research still needs to be completed from this thesis multiple directions can be taken in future studies. One direction could be to further address the endpoint accuracy and movement kinematic changes of upper limb reaching and determine if similar results in decreasing endpoint variability and modifying joint coordination can be found. Another direction could look to address the debate in the literature of having a SCM measure as a startle indicator. This will have significance on future StartReact methodologies and address the heterogonous samples.

Once the methodology in StartReact literature has been addressed and the potential uses have been studied future research could use StartReact in a rehabilitation protocol that monitors individuals' inter-joint coordination patterns, muscle activity, and functional improvement. Combined with an

optimal amount of variability approach, researchers could attempt to determine if functional movement patterns are emerging in response to training in this context.

6.4 Limitations

In both experimental studies the sample size was insufficiently powered, Chapter 4 *n* = 10 and Chapter 5 *n* = 12. This was largely due to recruitment restraints such as time remaining on the current degree due to the Covid-19 pandemic. To combat this in the results section non-parametric tests were reported. Results from both studies should be used as a platform for future research. The results provide a general direction for future research to explore by showing preliminary outcomes of PMT enhancements and coordination changes in an unconstrained reaching task.

Both experimental results also highlight methodological issues that should be addressed in future research. One being the use of a SCM measure as an indicator of startle. The discussion of Chapter 4 explains in detail an argument for not having a measure of startle, but this does not invalidate the claims in the literature that the faster PMT are correlated with an indicator of startle. A future study should use multiple dB levels to further study the difference in the stimulus intensity effect and StartReact effect. This would contribute to the StartReact methodology in determining a consistent dB level to be used in future studies.

Chapter 4 inclusion criteria required the stroke survivor to have a score of two or more on the oxford scale. This criterion was implemented due to the task being a button press task and participants lower than a two would not be able to press the button. By excluding the more severely impaired participants from the study this creates a limitation in the sample. Chapter 5 had no impairment level inclusion criteria, but also no measure of impairment level. StartReact methodology would benefit from having some measure of impairment because of the difficulty in generalizing to a population which is diverse in disability. This will provide the literature with the knowledge of which impairment levels

respond to the stimulus and which (if any) do not. It could also provide a target group within the stroke population that benefit from StartReact the most.

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Appendix A

Risk of Bias Questions

1. Was the study question or objective clearly stated?
2. Were eligibility/selection criteria for the study population prespecified and clearly described?
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?
4. Were all eligible participants that met the prespecified entry criteria enrolled?
5. Was the sample size sufficiently large to provide confidence in the findings?
6. Was the test/service/intervention clearly described and delivered consistently across the study population?
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Note. This tool is the original wording found in the NIH quality assessment tool (National Heart Lung and Blood Institute, 2021).

Appendix B

Covid-19 protocol Chapter 4

The Cybex lab was kept ventilated by leaving the windows open to decrease the chance of Covid-19 transmission. Covid-19 protocols were met by only allowing two people in the lab at one time, this included the participant and the researcher. 3 days prior to the testing day the researcher took a covid19 lateral flow test, and again on the day of testing to reduce the risk of covid-19 transmission. The participant was asked to complete a lateral flow test prior to coming to campus for testing.

On the day of testing support systems of the participants were asked to remain in the lobby of the Heinz Wolff building and continue to meet the protocols for covid-19 mitigation. Both the researcher and the participant wore masks and had their temperature taken upon entering the lab. The participants were also given a questionnaire to determine if they were feeling any symptoms related to covid-19. If the participants had a positive covid-19 test they were asked to remain at home and comply with government guidance. If the participants had a negative covid-19 test but exhibited an increased temperature and/or symptom of covid-19 they were asked to go back home and reschedule for a different date.

Appendix C

Oxford Scale for Muscle Strength (Kleyweg et al., 1991)

Grade	Muscle Activity
0	No visible contraction
1	Muscle movement with no joint movement
2	Movement of the limb but not against gravity
3	Movement against gravity
4	Movement against gravity and with some resistance
5	Full strength

Note. (Kleyweg et al., 1991)

Appendix D

MATLAB normalization code

```
A = normalize(AAPlotsML,"range", [-1,1])
```

Appendix E

MATLAB Code for Endpoint Calculations

```
tblA=sortrows(WG120I,'X','ascend'); %gets coordinates of the endpoints and sort
them ascendingly according to the colume with heading X (X-coordinate values),
and saves them in a table called tblA (endpoints 1-18 used below).
tblA=table2array(tblA); %converts tblA to an array with the same name, but having
x and z coordinates only.
tblA=tblA(:, [1,3]); % returns X and Z coordinates and saves them into variable
tblA.


xz_bar = mean(tblA);
RE = sqrt((xz_bar(1)^2)+(xz_bar(2)^2));




for i=1:length(tblA)
    AVE (i) = sqrt((tblA(i, 1)-xz_bar(1))^2 + (tblA(i, 2)-xz_bar(2))^2);
end
AVE = mean(AVE);



P1=tblA(1,:); % P1 - P18 are coordinates of the endpoints 1-8 for 18 different
reaches.
P2=tblA(2,:);
P3=tblA(3,:);
P4=tblA(4,:);
P5=tblA(5,:);
P6=tblA(6,:);
P7=tblA(7,:);
P8=tblA(8,:);
P9=tblA(9,:);
P10=tblA(10,:);
P11=tblA(11,:);
P12=tblA(12,:);
P13=tblA(13,:);
P14=tblA(14,:);
P15=tblA(15,:);
P16=tblA(16,:);
P17=tblA(17,:);
P18=tblA(18,:);
```

```
Numbers=[P1;P2;P3;P4;P5;P6;P7;P8;P9;P10;P11;P12;P13;P14;P15;P16;P17;P18];
x=Numbers(:,1);
y=Numbers(:,2);
scatter(x,y)
ax = gca;
ax.XAxisLocation = 'origin';
ax.YAxisLocation = 'origin';



X=tblA(:,1);
Y=tblA(:,2);
[TH,R] = cart2pol(X,Y);
TH_deg = rad2deg(TH);


for i=1:length(TH_deg)
    if TH_deg(i)<0
        TH_deg(i) = TH_deg(i)+360
    end
end
DE=mean(TH_deg);


a=tblA([1 2],:);
A=pdist(a,"euclidean"); %calculates vector distance between two endpoints. These
are sides of triangles used for calculation of the area of spread of endpoints.
b=tblA([1 3],:);
B=pdist(b,"euclidean");
c=tblA([2 3],:);
C=pdist(c,"euclidean");
S_1=(A+B+C)/2;
Area_1=sqrt(S_1*(S_1-A)*(S_1-B)*(S_1-C)); %gets area of the first triangle based
on endpoints 1-3.


a=tblA([2 3],:);
A=pdist(a,"euclidean");
b=tblA([2 4],:);
B=pdist(b,"euclidean");
c=tblA([3 4],:);
C=pdist(c,"euclidean");
S_2=(A+B+C)/2;
Area_2=sqrt(S_2*(S_2-A)*(S_2-B)*(S_2-C));


a=tblA([3 4],:);
```

```
A=pdist(a,"euclidean");
b=tblA([3 5],:);
B=pdist(b,"euclidean");
c=tblA([4 5],:);
C=pdist(c,"euclidean");
S_3=(A+B+C)/2;
Area_3=sqrt(S_3*(S_3-A)*(S_3-B)*(S_3-C));


a=tblA([4 5],:);
A=pdist(a,"euclidean");
b=tblA([4 6],:);
B=pdist(b,"euclidean");
c=tblA([5 6],:);
C=pdist(c,"euclidean");
S_4=(A+B+C)/2;
Area_4=sqrt(S_4*(S_4-A)*(S_4-B)*(S_4-C));


a=tblA([5 6],:);
A=pdist(a,"euclidean");
b=tblA([5 7],:);
B=pdist(b,"euclidean");
c=tblA([6 7],:);
C=pdist(c,"euclidean");
S_5=(A+B+C)/2;
Area_5=sqrt(S_5*(S_5-A)*(S_5-B)*(S_5-C));


a=tblA([6 7],:);
A=pdist(a,"euclidean");
b=tblA([6 8],:);
B=pdist(b,"euclidean");
c=tblA([7 8],:);
C=pdist(c,"euclidean");
S_6=(A+B+C)/2;
Area_6=sqrt(S_6*(S_6-A)*(S_6-B)*(S_6-C));


a=tblA([7 8],:);
A=pdist(a,"euclidean");
b=tblA([7 9],:);
B=pdist(b,"euclidean");
c=tblA([8 9],:);
C=pdist(c,"euclidean");
S_7=(A+B+C)/2;
Area_7=sqrt(S_7*(S_7-A)*(S_7-B)*(S_7-C));
```

```
a=tblA([8 9],:);
A=pdist(a,"euclidean");
b=tblA([8 10],:);
B=pdist(b,"euclidean");
c=tblA([9 10],:);
C=pdist(c,"euclidean");
S_8=(A+B+C)/2;
Area_8=sqrt(S_8*(S_8-A)*(S_8-B)*(S_8-C));


a=tblA([9 10],:);
A=pdist(a,"euclidean");
b=tblA([9 11],:);
B=pdist(b,"euclidean");
c=tblA([10 11],:);
C=pdist(c,"euclidean");
S_9=(A+B+C)/2;
Area_9=sqrt(S_9*(S_9-A)*(S_9-B)*(S_9-C));


a=tblA([10 11],:);
A=pdist(a,"euclidean");
b=tblA([10 12],:);
B=pdist(b,"euclidean");
c=tblA([11 12],:);
C=pdist(c,"euclidean");
S_10=(A+B+C)/2;
Area_10=sqrt(S_10*(S_10-A)*(S_10-B)*(S_10-C));



a=tblA([11 12],:);
A=pdist(a,"euclidean");
b=tblA([11 13],:);
B=pdist(b,"euclidean");
c=tblA([12 13],:);
C=pdist(c,"euclidean");
S_11=(A+B+C)/2;
Area_11=sqrt(S_11*(S_11-A)*(S_11-B)*(S_11-C));


a=tblA([12 13],:);
A=pdist(a,"euclidean");
b=tblA([12 14],:);
B=pdist(b,"euclidean");
```

```
c=tblA([13 14],:);
C=pdist(c,"euclidean");
S_12=(A+B+C)/2;
Area_12=sqrt(S_12*(S_12-A)*(S_12-B)*(S_12-C));


a=tblA([13 14],:);
A=pdist(a,"euclidean");
b=tblA([13 15],:);
B=pdist(b,"euclidean");
c=tblA([14 15],:);
C=pdist(c,"euclidean");
S_13=(A+B+C)/2;
Area_13=sqrt(S_13*(S_13-A)*(S_13-B)*(S_13-C));


a=tblA([14 15],:);
A=pdist(a,"euclidean");
b=tblA([14 16],:);
B=pdist(b,"euclidean");
c=tblA([15 16],:);
C=pdist(c,"euclidean");
S_14=(A+B+C)/2;
Area_14=sqrt(S_14*(S_14-A)*(S_14-B)*(S_14-C));


a=tblA([15 16],:);
A=pdist(a,"euclidean");
b=tblA([15 17],:);
B=pdist(b,"euclidean");
c=tblA([16 17],:);
C=pdist(c,"euclidean");
S_15=(A+B+C)/2;
Area_15=sqrt(S_15*(S_15-A)*(S_15-B)*(S_15-C));


a=tblA([16 17],:);
A=pdist(a,"euclidean");
b=tblA([16 18],:);
B=pdist(b,"euclidean");
c=tblA([17 18],:);
C=pdist(c,"euclidean");
S_16=(A+B+C)/2;
Area_16=sqrt(S_16*(S_16-A)*(S_16-B)*(S_16-C));
```

```
TSE=(Area_1+Area_2+Area_3+Area_4+Area_5+Area_6+Area_7+Area_8+Area_9+Area_10+Area_
11+Area_12+Area_13+Area_14+Area_15+Area_16); %gets Total Spread of Error as a
measure of total variability of endpoints.
format short
Answers=[RE AVE DE TSE]
```

Appendix F

Ethical Approval Chapter 4 with Covid Protocols

College of Health, Medicine and Life Sciences Research Ethics Committee (DLS)
Brunel University London
Kingston Lane
Uxbridge
UB8 3PH
United Kingdom

www.brunel.ac.uk

23 August 2021

LETTER OF APPROVAL

APPROVAL HAS BEEN GRANTED FOR THIS STUDY TO BE CARRIED OUT BETWEEN 23/08/2021AND 31/12/2022

Applicant (s): Ms Mara DeLuca

Project Title: Determination of Prepulse Inhibition and Prepulse Facilitation in Stroke Survivors (2)

Reference: 18927-A-Aug/2021- 33866-3

Dear Ms Mara DeLuca

The Research Ethics Committee has considered the above application recently submitted by you.

The Chair, acting under delegated authority has agreed that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- Please ensure compliance with Brunel's social distancing policy (as mentioned in your risk assessment, but not explicitly mentioned here). This is expected to be in force for the duration of Term 1 (i.e. the duration of this project).
- The amendments are fine thank you. Just note if the participant brings a guest they would be able to remain in the lab (HNZ036) following the Covid requirements: mask wearing, social distancing etc. This is probably better than them waiting somewhere else.
- **Approval is given for remote (online/telephone) research activity only. Face-to-face activity and/or travel will require approval by way of an amendment.**
- **The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee by way of an application for an amendment.**
- In addition to the above, please ensure that you monitor and adhere to all up-to-date local and national Government health advice for the duration of your project.

Please note that:

- Research Participant Information Sheets and (where relevant) flyers, posters, and consent forms should include a clear statement that research ethics approval has been obtained from the relevant Research Ethics Committee.
- The Research Participant Information Sheets should include a clear statement that queries should be directed, in the first instance, to the Supervisor (where relevant), or the researcher. Complaints, on the other hand, should be directed, in the first instance, to the Chair of the relevant Research Ethics Committee.
- The Research Ethics Committee reserves the right to sample and review documentation, including raw data, relevant to the study.
- You may not undertake any research activity if you are not a registered student of Brunel University or if you cease to become registered, including abeyance or temporary withdrawal. As a deregistered student you would not be insured to undertake research activity. Research activity includes the recruitment of participants, undertaking consent procedures and collection of data. Breach of this requirement constitutes research misconduct and is a disciplinary offence.

Professor Louise Mansfield

Chair of the College of Health, Medicine and Life Sciences Research Ethics Committee (DLS)

Brunel University London

Appendix G

Ethical Approval Chapter 5

College of Health, Medicine and Life Sciences Research Ethics Committee (DLS)
Brunel University London
Kingston Lane
Uxbridge
UB8 3PH
United Kingdom

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1 December 2022

LETTER OF APPROVAL

APPROVAL HAS BEEN GRANTED FOR THIS STUDY TO BE CARRIED OUT BETWEEN 01/12/2022 AND 31/12/2023

Applicant (s): Ms Mara DeLuca Dr Amir Mohagheghi

Project Title: Movement Variability in StartReact

Reference: 39806-MHR-Nov/2022- 41982-2

Dear Ms Mara DeLuca

The Research Ethics Committee has considered the above application recently submitted by you.

The Chair, acting under delegated authority has agreed that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- Please use your approved study dates (above) in all your study documents.
- Please add to the advert that your study has been approved by the College of Health, Medicine and Life Sciences Research Ethics Committee and your approved study dates. If you will use any further text to distribute your flyer (eg an email), please submit this for approval via an amendment.
- Please note, you must use the Bcc function to send emails to multiple recipients.
- Please add your study dates to your consent form.
- D29 - Please note, it is recommended that data is stored on a Brunel password protected server.
- D30 - Please ensure that you have agreed a potential course of action with your supervisor in advance in case of this eventuality.
- **The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee by way of an application for an amendment.**
- **Please ensure that you monitor and adhere to all up-to-date local and national Government health advice for the duration of your project.**

Please note that:

- Research Participant Information Sheets and (where relevant) flyers, posters, and consent forms should include a clear statement that research ethics approval has been obtained from the relevant Research Ethics Committee.
- The Research Participant Information Sheets should include a clear statement that queries should be directed, in the first instance, to the Supervisor (where relevant), or the researcher. Complaints, on the other hand, should be directed, in the first instance, to the Chair of the relevant Research Ethics Committee.
- Approval to proceed with the study is granted subject to receipt by the Committee of satisfactory responses to any conditions that may appear above, in addition to any subsequent changes to the protocol.
- The Research Ethics Committee reserves the right to sample and review documentation, including raw data, relevant to the study.
- If your project has been approved to run for a duration longer than 12 months, you will be required to submit an annual progress report to the Research Ethics Committee. You will be contacted about submission of this report before it becomes due.
- You may not undertake any research activity if you are not a registered student of Brunel University or if you cease to become registered, including abeyance or temporary withdrawal. As a deregistered student you would not be insured to undertake research activity. Research activity includes the recruitment of participants, undertaking consent procedures and collection of data. Breach of this requirement constitutes research misconduct and is a disciplinary offence.

Professor Louise Mansfield

Chair of the College of Health, Medicine and Life Sciences Research Ethics Committee (DLS)

Brunel University London

Appendix H

Published Systematic Review

J Neurophysiol 127: 938–945, 2022.
First published March 2, 2022; doi:10.1152/jn.00392.2021

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SYSTEMATIC REVIEW

A systematic review with meta-analysis of the StartReact effect on motor responses in stroke survivors and healthy individuals

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Abstract

Control of limb movements may be impaired after stroke due to the loss of connectivity between the cerebral cortex and spinal cord. A notion to improve motor function in stroke survivors is to use alternate motor fibers, such as the reticulospinal tract (RST), which originate from the brainstem and terminate at different levels of spinal cord. One way of targeting the RST is to use a "StartReact" protocol to foster premature release of a preplanned movement in response to a startling stimulus. Our aim was to find support for the preservation of such StartReact effect in stroke survivors. We conducted a systematic review with meta-analysis of literature published in English up to September 2020, to explore differences in motor responses to startling stimuli in StartReact effects. Protocol of the study was registered (PROSPERO Registration No. CRD42020191581). PubMed, Google Scholar, Web of Science, PsycINFO, and Science Direct were searched for relevant literature. The meta-analysis contained six studies involving a total of 151 stroke and healthy participants. Muscle onset latency data were extracted from the qualifying studies and compared using RevMan. StartReact effect was present in both stroke and healthy groups, represented by shortened muscle onset latency when startling stimulus was present. There was considerable heterogeneity of the outcome measures, which was attributed to the range of motor impairments among stroke survivors and methodologies used. Our findings support the notion of preservation of preprogramming ability and suitability of RST and StartReact effect for motor rehabilitation following stroke.

neurorehabilitation; reaction time; StartReact; stroke; stroke rehabilitation

INTRODUCTION

Stroke is a leading cause of movement disability (1). In the UK alone, there are 1.2 million stroke survivors, two-thirds of whom live with a disability secondary to stroke (1). The type and severity of motor disability caused by stroke is varied, and there is an urgent need to develop new rehabilitation methods to help improve motor disability in stroke survivors. Many neurophysiological characteristics have been investigated to identify and use features that might be exploited to improve stroke rehabilitation outcomes. One such characteristic is the startle response (2) and StartReact effect. Investigations looking into the StartReact effect have peaked interests across multiple clinical populations such as hereditary spastic paraplegia (3), stroke (4–11), and Parkinson's disease (12). These populations exhibit faster reaction times in StartReact effects despite the apparent motor impairment that could be attributed to motor programming and/or the execution of the movement (4, 5, 11).

In a simple reaction time (RT) experimental context, the premature release of a preprogrammed motor response elicited by a startling (mostly loud auditory) stimulus, delivered simultaneously with the imperative "go" signal, is called the StartReact effect (2). It has been suggested that the startling stimulus excites the subcortical structures, and the prepared action is released with a shorter latency when compared with movements without startle. In contrast to classical reaction time literature, StartReact literature uses electromyography (EMG) onset latency of the agonist muscle (premotor time) as a measure of RT (4), and the presence of StartReact effect can therefore help elucidate whether the participant has maintained motor programming ability (4, 5). Several studies specifically refer to the involvement of the reticulospinal tract (RST) in the shortening of the premotor time (PMT) and associated RT in producing StartReact effect (3, 4, 10, 13, 14). This is important to stroke survivors with residual motor impairments because the RST is sometimes spared, and as indicated earlier, might be a target of rehabilitation aimed at improving motor function (9). Specifically, the presence of StartReact effect in stroke survivors can be a biomarker for the preservation of motor programming ability and involvement of RST in movement execution, which

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