A Systematic Review with Meta-analysis of the StartReact Effect on Motor Responses in Stroke Survivors and Healthy Individuals

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Abstract

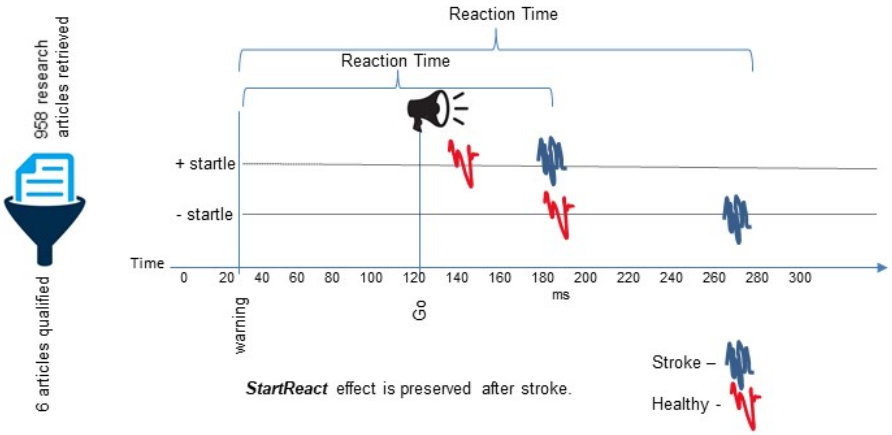
Introduction: Control of limb movements may be impaired after stroke due to the loss of connectivity between the cerebral cortex and spinal cord. A notion to improve motor function in stroke survivors is to employ alternate motor fibers, such as the reticulospinal tract (RST), which originate from the 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 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. 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 notion of preservation of preprogramming ability and suitability of RST and StartReact effect for motor rehabilitation following stroke.

Keywords

StartReact, Neurorehabilitation, stroke, stroke rehabilitation, reaction time



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35 **Conflicts of interest/Competing interests (include appropriate disclosures)**
36 The authors declare that they have no conflict of interest.

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 employ 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 (12). These populations exhibit faster reaction times in StartReact effects despite the apparent motor impairment which 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 to 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 above, 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 in turn could serve as a possible alternate motor pathway for neurorehabilitation (5).

Presence of startle responses are determined by EMG in the Sternocleidomastoid muscle (SCM) and/or orbicularis oculi muscle (OOC) muscles (2,4,15-17). 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 reaction time in trials where there is a SCM startle response than when there is no response shown by the SCM (15-17). 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 (15) [20].

The purpose of this systematic review with meta-analysis was to review published literature on StartReact and assess the strength of evidence for StartReact effect in stroke survivors and healthy individuals. 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. This systematic review could therefore make a stronger case for the preservation of StartReact in stroke survivors (if any) by combining reaction times of smaller studies. Furthermore, it could advise on the estimation of StartReact Effect Size and elucidate methodological differences which could have confounded results from previous studies. The present 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, it also allowed inclusion of studies that used either measure.

Methodology

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: reaction time, startle reflex, and StartReact. The development of the keywords followed PICO (Population, Intervention, Comparison, and Outcome) (18) 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 nonclinical 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 orbicularis oculi OOC, and/or premotor time (reaction time) measurements determined by sEMG of the main muscle of the limbs used in the motor response. Meta-analysis was performed using the reaction time measurements to assess the strength of evidence for StartReact effect. We were aware of the difference between the definitions of premotor and reaction times in classical reaction time 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* (19) 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 (MD, AM) independently for inclusion in the review. 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 (DL) 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 automatic postural responses 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.

Mean and standard deviation 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 (20). In 5 studies, the measurements of EMG onset time came from the upper limb. One study (6), 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 (21). 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.

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, 9 articles were excluded leaving 6 studies to be included in the qualitative synthesis and meta-analysis. Figure 1 is a flow diagram outlining the study selection process.

Insert Figure 1 Here

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 2 studies (7-8) 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 2 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

Characteristics of Included Studies Table

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 Affected side was the dominant arm before stroke	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) 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	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**

	Arm hemiparesis Ability to perform reaching movement	**ms** with respect to Go.

Note: Loud Auditory Stimulus (LAS). 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. 2 studies (7-8) 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 1 study (8) 1 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 (9) 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 3 of the reviewed studies (6-8), 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 (9). 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 reaction time 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 reaction time 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, reaction time data for trials without starting stimulus for one paper (7) 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.

Insert Figure 2 Here

In the healthy group, the mean difference in reaction time between conditions with and without startling stimulus was -42.22ms (95%CI: -60.05, -24.39). This was representative of a decrease in reaction time 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.

Insert Figure 3 Here

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 (reaction time) of the startling stimuli. This is the first study to systematically search the literature for the StartReact effect in stroke survivors. For both groups, reaction time decreased when a loud auditory stimulus was present compared to trials with no loud stimuli (Figures 2 and 3).

The stroke group showed a much larger mean reaction time difference (more than double), between trials with and without startling stimulus, compared to the healthy group (-86.72ms vs. -42.22ms). As a result of the larger mean reaction time 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 (RST) in motor responses in StartReact effects (4-6, 13), but also the notion that the larger reduction in RT in stroke survivors was due to compromised corticospinal tract (CST) (10).

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 (18). 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 2 studies (5, 10) which had a rating of '*Good*', and the other group with 4 studies (6-9) 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 -107.50ms (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 [$I^2 = 75\%$; -68.22ms (95%CI: -138.32, 1.89)] and healthy [$I^2 = 75\%$; -40.95ms (95%CI: -68.63, -13.27)] groups.

Insert Figure 4 Here

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 2 studies (McCombe Waller et al. 2016, Yang et al. 2019) (7-8) reported how they measured the acoustic stimulus intensity in their methods. Carlsen et al. 2007 (15) 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 analyses (below).

In the 6 qualified studies, there can be a subgroup created based on the presence of SCM muscle activity as an indicator of startle. Analyses 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, Tresch, & Perreault (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 -96.90ms and a 95%CI [-168.87, -24.93]. The healthy group with a SCM measure showed a mean difference of -52.73ms and a 95%CI [-82.44, -23.02]. The stroke group without a measure of SCM showed a mean difference of -77.67ms and a 95%CI [-111.38, -43.97]. The healthy group without a measure of SCM showed a mean difference of -30.11ms and a 95%CI [-53.71, -6.52].

To calculate the sample sizes after subgrouping data based on the presence of SMC 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) (25) 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 (15).

To determine a more appropriate and effective protocol to elicit StartReact in stroke survivors, other factors such as prepulse inhibition (PPI) and prepulse facilitation (PPF) should also be considered. For example, in all studies except one (10), a '*warning*' cue was employed and followed by an interstimulus interval (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 (23). Extensive work has been done on the inhibitory effect, but little has been done on the faciliatory effect of the ISI (24). In the included studies in the present review, the ISI varied between 1 and 3.5s. 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 (10), 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.

Conclusion

While the CST is the main pathway for voluntary motor control, the RST is known to work simultaneously with and alongside the CST in some movements (26). The RST is known to project to areas of the spinal cord along similar projections as the CST (26). StartReact literature provides evidence that the neural pathways needed to elicit a StartReact response may remain intact after stroke (5-6). 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 RST for motor rehabilitation following stroke. It also highlights the scarce amount of data in StartReact effects 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.

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Appendix A

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 (21).

Legends

Figure 1. PRISMA 2009 Flow Diagram (22) illustrating study selection process. Of the 9 articles excluded, 7 were due to study design, 1 was due to methodology, and 1 was due to reaction time measures not meeting inclusion criteria.

Figure 2. Outcome of meta-analysis on the means and standard deviations of reaction time (EMG onset latency of the main agonist muscle) for stroke survivors. Data collected via email (10, 8). No response received to our request for further data (7).

Figure 3. Outcome of meta-analysis on the means and standard deviations of reaction time (EMG onset latency of the main agonist muscle) for healthy individuals. Missing data collected via email (10,8).

Figure 4. 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.