

## **Chieh-ling Yang, MS, OT**

PhD Candidate, Department of Physical Therapy and Rehabilitation Science  
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### **EDUCATION**

2011-2018	University of Maryland Baltimore	PhD in Physical Rehabilitation Science
2008-2010	Chang Gung University, Taiwan	MS in Occupational Therapy
2004-2008	National Taiwan University, Taiwan	BS in Occupational Therapy

### **RESEARCH EXPERIENCE**

#### **University of Maryland Baltimore**

2016- **Principal Investigator**

Present Study title: "Cortical enhancement of posture and movement planning, initiation, and execution during standing voluntary reach following stroke"

(Doctoral thesis, funded by the American Heart Association)

Advisors: Sandy McCombe Waller and Mark W. Rogers

2013-2017 **Research Assistant**

Study title: "A comparison of reactive and voluntary lateral step training to improve balance and reduce falls in persons post-stroke" (PI: Vicki L. Gray)

- Collection of kinematic (Vicon), force platforms (AMTI), EMG data, and muscle strength testing (biodesx) in stroke subject and older adults

- Assistance in reactive and voluntary step training in stroke subjects

2012-2016 **Research Assistant/ Trainer**

Study title: "Intervention to enhance lateral balance function and prevent falls in aging"

(PI: Mark W. Rogers)

- Subject training including strength training, reactive step training, and stretching

- IRB compliance reporting

## **Chang Gung University, Taiwan**

- 2010-2011 **Research Assistant**, Motor Control and Behavior Analysis Lab (PI: Ching-yi Wu)  
- Analysis of clinical outcome measures and kinematic data for upper extremity tasks in stroke subjects and preparation of manuscripts
- 2008-2010 **Graduate Research Assistant**  
Study title: “Unilateral versus bilateral robot-assisted training in stroke patients: Effects on upper extremity performance and functional ability” (Master thesis)  
Advisor: Ching-yi Wu  
- IRB applications, subject screening, recruitment, subject training, analysis of clinical outcome measures and kinematic data

## **GRANT SUPPORT**

### **Active Grants**

- 2016-2018 (PI: Yang)  
**“Cortical enhancement of posture, movement planning, and execution during standing voluntary reach following stroke“**  
Grant# 16PRE29970004  
American Heart Association MAA Winter 2016 Predoctoral Fellowship  
Annual Direct Costs: \$25,950  
Total Direct Costs: \$51,900

## **HONORS AND AWARDS**

- 2014-2017 **Graduate School Travel Fellowship** - \$300/yr, University of Maryland Baltimore, MD
- 2016 **Best Poster Award**, Gray V. L., Yang, C.-L., McCombe Waller, S., & Rogers, M. W. (2016, Nov). *The influence of sensorimotor deficits on unexpected lateral perturbations after stroke*. APTAs of Maryland, DC, and Delaware Annual Conference, College Park, MD
- 2011 **Studying Abroad Scholarship** - \$16,000, The Ministry of Education of Taiwan, Taiwan
- 2010 **Honorary member of Phi Tau Phi Society**, Chang Gung University, Taoyuan, Taiwan
- 2009 **OTUROC Bronze Poster Award**, Yang, C.-L., Lin, K.-C., Chen, H.-Y., Chen, H.-Y., Chao, P.-C., Lin, P.-C., & Wu, C.-Y. (2009, June). *Effects of robot-assisted therapy in stroke patients: A literature review*. Occupational Therapist Union, ROC (OTUROC) Conference, Taipei, Taiwan

- 2008, 2009 **Presidential Award** - \$ 3000/yr, Chang Gung University, Taoyuan, Taiwan  
Top 5% student in the Occupational Therapy Class
- 2007 **Presidential Award**, National Taiwan University, Taipei, Taiwan  
Top 5% student in the Occupational Therapy Class

### **COMMITTEES**

- 2015-2016 **Student Representative for Physical & Rehabilitation Science Program**, Graduate Student Association, University of Maryland Baltimore, MD
- General responsibility: Communicate student concerns and ideas on matters that affect graduate student life, support graduate student research interests, review and decide student groups budget applications, plan annual Graduate Research Conference, and new student orientation
  - Treasury Committee: review and grade travel fellowships applications

### **PROFESSIONAL SOCIETY MEMBERSHIPS**

- 2015-present Member of the Society for Neuroscience
- 2015-present Member of the American Heart Association

### **TEACHING SERVICE**

#### **University of Maryland Baltimore**

- 2015-2017 **Lab Assistant**  
Neuromuscular I Course (DPTE 524)  
65 Doctor of Physical Therapy students (2<sup>nd</sup> year) - 4 contact hours/yr  
**Content:** Stroke Rehabilitation Research
- 2013-2017 **Seminar facilitator**  
Neuromuscular I Course (DPTE 524)  
13 Doctor of Physical Therapy students (2<sup>nd</sup> year) - 4-6 contact hours/yr  
**Content:** Evidence-based practice and research methods
- 2011-2012 **Lecturer and Lab Assistant**  
Basic Science II (DPTE 513)  
65, 1<sup>st</sup> year Doctor of Physical Therapy students (1<sup>st</sup> year) - 3 contact hours/yr  
**Content:** Aging effects on balance, gait, and cognition (Lecture)  
Older Adult and Aging upper extremity clinical assessments (Lab)

#### **Chang Gung University**

- 2008-2009 **Teaching assistant** - Research Methodology Course (Role: Grading)

## CLINICAL EXPERIENCE

- 2007-2008      Clinical practice of occupational therapy internships (3 months for each)
- Taipei Hospital, Ministry of Health and Welfare (adults physical disability OT clinic)
  - National Taiwan University Hospital (pediatric OT clinic)
  - Taipei City Psychiatric Center (psychiatric OT clinic)

## PROFESSIONAL LICENSURE

Active            License of Occupational Therapist in Taiwan

## PUBLICATIONS

### **Peer-reviewed Journal Articles**

1. Impaired posture, movement preparation, and execution during standing reaching in people with chronic stroke. (In preparation).
2. Effect of transcranial direct current stimulation on posture, movement planning, and execution during standing voluntary reach following stroke. (In preparation).
3. Gray, V. L., **Yang, C.-L.**, McCombe Waller, S., & Rogers, M. W. (2017). Lateral perturbation induced stepping: Strategies and predictors in persons post-stroke. *Journal of Neurological Physical Therapy (ranked 15/135 Rehabilitation journals in Web of Science)*, 41(4), 222-228. doi: 10.1097/NPT.0000000000000202.
4. McCombe Waller, S., **Yang, C.-L.**, Magder, L., Yungher, D., Gray, V. L., & Rogers, M. W. (2016). Impaired motor preparation and execution during standing reach in people with chronic stroke. *Neuroscience Letters*, 630, 38-44. doi: 10.1016/j.neulet.2016.07.010.
5. Wu, C.-Y., **Yang, C.-L.**, Chen, M.-D., Lin, K.-C., & Wu, L.-L. (2013). Unilateral versus bilateral robot-assisted rehabilitation on arm-trunk control and functions post stroke: A randomized controlled trial. *Journal of NeuroEngineering and Rehabilitation (ranked 3/135 Rehabilitation journals in Web of Science)*, 10:35 (10 pages). doi: 10.1186/1743-0003-10-35.
6. Wu, C.-Y., **Yang, C.-L.**, Chuang, L.-L., Lin, K.-C., Chen, H.-C., Chen, M.-D., & Huang, W.-C. (2012). Effect of therapist-based versus robot-assisted bilateral arm training on motor control, functional performance, and quality of life after chronic stroke: a clinical trial. *Physical Therapy (ranked 11/135 Rehabilitation journals in Web of Science)*, 92(8), 1006-16. doi: 10.2522/ptj.20110282.
7. **Yang, C.-L.**, Lin, K.-C., Chen, H.-C., Wu, C.-Y., & Chen, C.-L. (2012). Pilot comparative study of unilateral and bilateral robot-assisted training on upper-extremity performance in patients with stroke. *American Journal of Occupational Therapy (ranked 24/135 Rehabilitation journals in Web of Science)*, 66(2), 198-206. doi: 10.5014/ajot.2012.003103.

8. **Yang, C.-L.**, Lin, K.-C., Chen, H.-Y., Chen, H.-Y., Chao, P.-C., Lin, P.-C., & Wu, C.-Y. (2009). Effects of robot-assisted therapy in stroke patients: A literature review. *Journal of Taiwan Occupational Therapy Research and Practice*, 5, 128-144.
  9. Huang, W.-C., **Yang, C.-L.**, Wu, C.-Y., & Lin, K.-C. (2009). Effects of different bilateral arm training in stroke rehabilitation: A literature review. *Journal of Taiwan Occupational Therapy Association*, 27, 29-48.
- Complete List of Published Work in My Bibliography:** <https://goo.gl/8buZfL>

## CONFERENCES

### **International**

1. McCombe Waller, S., Howe (Gaeta), A., **Yang, C.-L.**, Magder, L., & Rogers, M. W. (2013, June). *Subcortical and cortical contributions to posture and movement planning and preparation for forward reaching in standing post stroke*. Poster presentation at the Joint World Congress of International Society for Posture & Gait Research (ISPGR) and Gait and Mental Function, Akita, Japan.

### **National**

1. **Yang, C.-L.**, McCombe Waller, S., Rogers, M. W., & Gray, V. L. (2016, Nov). *The effects of reactive and voluntary step training on balance recovery during lateral perturbation in individuals with chronic stroke*. Poster presented at the annual meeting of the Society for Neuroscience, San Diego, CA
2. Gray, V.L., **Yang, C.-L.**, Obah, A., McCombe Waller, S., & Rogers, M. W. (2016, Nov). *Lateral balance control after stroke: A comparison of voluntary and perturbation induced stepping reactions*. Poster presented at the annual meeting of the Society for Neuroscience, San Diego, CA
3. **Yang, C.-L.**, Gray, V. L., Fujimoto, M., McCombe Waller, S., & Rogers, M. W. (2015, Oct). *Reactive and voluntary stepping in individuals with stroke: A comparison between paretic and nonparetic leg responses*. Poster presented at the annual meeting of American Society of Neurorehabilitation and annual meeting of Society for Neuroscience, Chicago, IL.
4. Gray V. L., **Yang, C.-L.**, McCombe Waller S., & Rogers M. W. (2015, Oct). *Associations between foot cutaneous sensation and muscle activation patterns during unexpected lateral perturbations after stroke*. Poster presented at the annual meeting of American Society of Neurorehabilitation and annual meeting of Society for Neuroscience, Chicago, IL.
5. Inacio, M., Gray, V. L., Bair, W., **Yang, C.-L.**, Sanders, O., Abarro, J., Gaeta, A., Prettyman, M., Creath, R., McCombe-Waller, S., & Rogers, M.W. (2015, Feb). *Combining high intensity lateral balance training with resistance training to improve muscle performance in older people*. Poster presented at the American Physical Therapy Association Combined Sections Meeting, Indianapolis, IN.

6. **Yang, C.-L.**, McCombe Waller, S., Howe (Gaeta), A., & Rogers, M. W. (2013, Nov). *A Loud acoustic stimulus evoked-response during movement planning facilitates voluntary reach in patients with chronic stroke*. Poster presented at the annual meeting of Society for Neuroscience, San Diego, CA.
7. **Yang, C.-L.**, Lin, K.-C., Huang, W.-C., Hsieh, Y.-W., Liao, W.-W. & Wu, C.-Y. (2011, April). *Robot-assisted trainings for upper extremity rehabilitation after stroke: Unilateral vs. bilateral protocols*. Poster presented at the American Occupational Therapy Association (AOTA) Annual Conference & Expo, Philadelphia, PA.
8. **Yang, C.-L.**, Wu, C.-Y., Yu, H.-W. & Lin, K.-C. (2010, Nov). *Robot-assisted training for the rehabilitation of upper-limb muscle performance after stroke*. Oral presentation at the 29th Taiwan Occupational Therapy Association (TOTA) Conference, Taipei, Taiwan.
9. **Yang, C.-L.**, Yu, H.-W., Lin, K.-C., & Wu, C.-Y. (2010, June). *Devices-assisted movement training of upper extremity in stroke patients: A pilot study*. Poster presented at the Occupational Therapist Union, ROC (OTUROC) Conference, Tainan, Taiwan.
10. **Yang, C.-L.**, Lin, K.-C., Chen, H.-Y., Chen, H.-Y., Chao, P.-C., Lin, P.-C., & Wu, C.-Y. (2009, June). *Effects of robot-assisted therapy in stroke patients: A literature review*. Poster presented at the Occupational Therapist Union, ROC (OTUROC) Conference, Taipei, Taiwan.
11. Huang, W.-C., **Yang, C.-L.**, & Wu, C.-Y. (2009, June). *A literature review on symmetrical and asymmetrical bilateral arm training for stroke patients*. Poster presented at the Occupational Therapist Union, ROC (OTUROC) Conference, Taipei, Taiwan.

### **Local**

1. **Yang, C.-L.**, Rogers, M. W., & McCombe-Waller, S. *Impaired posture and movement preparation during standing voluntary reach in the paretic and nonparetic arms following stroke*. (2018, March). Poster presented at the annual University of Maryland Baltimore Graduate Research Conference, Baltimore, MD
2. Gray, V. L., **Yang, C.-L.**, Obah, A., McCombe Waller, S., & Rogers, M. W. (2017, March). *Lateral balance control after stroke: A comparison of voluntary and perturbation induced stepping reactions*. Poster presented at the annual University of Maryland Baltimore Graduate Research Conference, Baltimore, MD
3. **Yang C.-L.**, Gray, V. L., McCombe Waller, S., & Rogers, M. W. (2016, Nov). *Reactive and voluntary stepping in individuals with stroke: A comparison between paretic and nonparetic leg responses*. Poster presented at the American Physical Therapy Association of Maryland, DC, and Delaware Regional Annual Conference, College Park, MD.

4. Gray V. L., **Yang, C.-L.**, McCombe Waller, S., & Rogers, M. W. (2016, Nov). *The influence of sensorimotor deficits on unexpected lateral perturbations after stroke*. Poster presented at the APTAs of Maryland, DC, and Delaware Annual Conference, College Park, MD.
5. **Yang, C.-L.**, Gray, V. L., McCombe Waller, S., & Rogers, M. W. (2016, March). *The effects of reactive and voluntary step training on balance recovery during lateral perturbation in individuals with chronic stroke*. Poster presented at the annual University of Maryland Baltimore Graduate Research Conference, Baltimore, MD.
6. **Yang, C.-L.**, Gray, V. L., Fujimoto, M., McCombe Waller, S., & Rogers, M. W. (2015, March). *Reactive and voluntary stepping in individuals with stroke: A comparison between paretic and nonparetic leg responses*. Poster presented at the annual University of Maryland Baltimore Graduate Research Conference, Baltimore, MD.
7. **Yang, C.-L.**, McCombe Waller, S., Howe(Gaeta), A., & Rogers, M. W. (2014, March). *Acoustic stimulus evoked-response during movement planning facilitates voluntary reach in patients with chronic stroke*. Poster presented at the annual University of Maryland Baltimore Graduate Research Conference, Baltimore, MD.
8. McCombe-Waller, S., Howe(Gaeta), A., **Yang, C.-L.**, & Rogers, M. W. (2013, April). *Task-oriented arm training in standing improves both anticipatory postural control and upper extremity functional outcomes in stroke patients*. Poster presented at the annual University of Maryland Baltimore Graduate Research Conference, Baltimore, MD.

## **Abstract**

Title of Dissertation: Cortical enhancement of posture and movement planning, initiation, and execution during standing voluntary reach following stroke

Chieh-ling Yang, Doctor of Philosophy, 2018

Dissertation Directed by: Sandy McCombe Waller, Associate Professor, Department of Physical Therapy and Rehabilitation Science, University of Maryland School of Medicine, Baltimore, MD.

Stroke is the leading cause of disability and diminished quality of living that frequently includes impairments of postural control and upper extremity (UE) function. The ability to maintain balance while performing skillful reaching during everyday activities, requires appropriate sequencing of anticipatory postural adjustments (APAs) that normally precede and accompany the focal movement. Although these abilities are frequently compromised after stroke, the interaction of posture and upper extremity movement coupling (APA-reach sequence) in terms of planning, initiation, and execution is not well understood. Movement planning and preparation of APA-reach sequence was examined by SR responses elicited by a loud acoustic stimulus (LAS). After an instructed delayed period, subjects performed a standing reaching task in response to a “go” light cue. An LAS of 123 dB was randomly delivered at – 500, – 200, and 0 ms relative to the go cue. Kinetic, kinematic, and EMG data were recorded to characterize APA-reach movement response. In Chapter 2, we investigated the motor preparation and execution of paretic arm reaching during standing using an LAS to elicit a StartReact response of the APA-Reach sequence in adults with chronic hemiparesis and healthy age-matched

controls. The main finding was that subjects with stroke, demonstrated a marked reduction in the occurrence of the SR responses for both APA and forward reach at all LAS time points indicating movement planning and preparation dysfunction. In Chapter 3, we further investigated whether the deficits are system-wide to both the lesioned and contralesional sides or are by comparing the SR responses during the paretic and nonparetic arm movements. We found that individuals with stroke demonstrated system-wide deficits in posture and movement planning, preparation, and execution of APA-reach sequence as shown by significant reduction in the incidence of SR response and impaired APA-reach performance compared to healthy controls. Moreover, use of trunk compensation strategy as characterized by greater involvement of trunk and pelvic rotation was utilized by individuals with stroke during the paretic arm reaching compared to the nonparetic arm reaching and healthy controls. In Chapter 4, we investigated cortical enhancement effects of tDCS on posture and movement planning, initiation, and execution as measured by SR responses in individuals with stroke and healthy controls. The main finding from Chapter 4 was that stroke-related deficits in movement planning as shown by an abnormal absence of SR responses during the paretic arm reaching can be improved by application of anodal tDCS over the region of lesioned M1 and the enhancement effects are depending on the timing of the LAS.

Cortical enhancement of posture and movement planning, initiation, and execution during standing voluntary reach following stroke

by  
Chieh-ling Yang

Dissertation submitted to the Faculty of the Graduate School of the  
University of Maryland, Baltimore in partial fulfillment  
of the requirements for the degree of  
Doctor of Philosophy  
2018

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## **DEDICATION**

I would like to dedicate this work to my parents, I-ming Yang and Fan-chi Tseng, my brother, Shen-han Yang, and my husband, Thomas Shen.

## ACKNOWLEDGEMENTS

First, I would like to acknowledge my advisors, Dr. Sandy McCombe Waller and Dr. Mark Rogers. Without Dr. Sandy McCombe Waller's guidance, support, and encouragement, I would not have been able to accomplish this dissertation project. She inspired me a lot on research, interacting with subjects, IRS compliance, and manuscript writing. I am lucky to have her supervision during my intellectual and professional development. I would like to thank my senior advisor, Dr. Mark Rogers for his guidance on research. I appreciate him sharing knowledge on postural control and startle response with me. These discussions have inspired and motivated me on my dissertation project and future research directions. I also want to thank them for being my sponsors for the AHA grant and providing great inputs for the research proposal.

I would like to thank my dissertation committee members for taking their time to be part of my committee. Specifically, I would like to thank Dr. Gad Alon for offering help and expertise on tDCS, especially his comments on Chapter 4. I would like to thank Dr. Larry Magder for his promptness in helping with my statistical analysis questions. I would like to thank Dr. Doug Savin for being the reader on my committee and great suggestions.

I would like to thank all the PTRS faculty, research associates, and postdocs for their invaluable suggestions on my research projects, seminar presentation, and personal development. Specifically, I would like to thank Dr. Larry Forrester and Dr. Jill Whitall for their excellent work as successive Director of PhD Program. I would like to thank Dr. Vicki Gray for teaching me a lot on EMG and providing suggestions on my research projects and professional development. I enjoy the time being part of her stroke stepping project and also learn a lot from it. I would like to thank Dr. Rob Creath for his assistance on Matlab programming and experimental setup. Without his support, I would not be able to start data collection and conduct data analysis. I would also like to thank Dr. HaoYuan Hsiao for offering his help during my data collection.

I would like to express thanks to all of the PTRS staff in the Department of Physical Therapy and Rehabilitation Science for all the help and support through these

seven years. I would like to thank Terry Heron for helping me with registration when I first came to the program, Monica Martinez for her help with the AHA grant application, Jeff Hawk and Angel Chavez for their support on technology issues, and Surekha Vishwasrao for her help on accounting support for the AHA grant. I would like to thank Doug Pizac and Andrea Obah for their timely assistance when I needed help with data collection. I would like to thank Janice Abarro for being a great coordinator for the LIFT training team, and offering help, support, encouragement, and advice anyway she could.

I would like to thank all the fellow PhD students for all the collaboration, discussion, and piloting along the way. Specifically, I would like to thank Wan-wen Liao for her help during data collection and subjects recruiting.

I would like to recognize all my lovely study participants. Without their time and effort on participating in this project, I would not be able to complete this project. It is my pleasure and honor to work with these friendly and energetic participants.

I would like to acknowledge the American Heart Association and the Department of Physical Therapy and Rehabilitation Science for their financial support of this project.

Lastly, I would like to thank my parents, brother, my husband, and friends. Without my parents' support, I would not be the person I am today and would not be able to come so far getting a PhD. Without my brother accompanying my parents in Taiwan while I am away in the United States, I would not be able to concentrate on my research projects. I would like to thank my husband for his support through my graduate education. Without numerous piloting on him on weekends, I would not be able to be comfortable collecting data on my participants. I would like to thank all my friends in Taiwan and the United States for accompanying me and cheering me up throughout this process.

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## **LIST OF ABBREVIATIONS**

ABC: Activities Balance Confidence

APA: Anticipatory postural adjustment

AMT: Active motor threshold

BB: Biceps brachii

BERG: Berg Balance Scale

CB&M: Community Balance and Mobility Scale

CNS: Central nervous system

CoM: Center of mass

CoP: Center of Pressure

Dom: Dominance

EMG: Electromyography

FM: Fugl-Meyer Assessment

GFR: Ground reaction force

LAS: Loud acoustic stimulus

LE: Lower extremity

OOC: Orbicularis oculi

M1: Primary motor cortex

MD: middle deltoid

MEP: Motor-evoked potential

PMA: Premotor areas

PMC: Premotor cortex

PMRF: Pontomedullary reticular formation

SCM: Sternocleidomastoid muscle

SMA: Supplementary motor area

SOL: Soleus

SR: StartReact

tDCS: Transcranial direct current stimulation

TA: Tibialis anterior

TMS: Transcranial magnetic stimulation

UE: Upper extremity

WMFT: Wolf Motor Function Test

# **1 CHAPTER I. INTRODUCTION AND BACKGROUND**

## **1.1 Introduction**

Stroke is the leading cause of disability and diminished quality of living that frequently includes impairments of postural control and upper extremity (UE) function (Nakayama, Jorgensen, Raaschou, & Olsen, 1994; Tyson, Hanley, Chillala, Selley, & Tallis, 2006). For example, the ability to maintain balance while performing skillful reaching during everyday activities requires appropriate sequencing of anticipatory postural adjustments (APAs) that normally precede and accompany the focal movement. Although these abilities are frequently compromised after stroke, the interaction of anticipatory posture and UE movement coupling (APA-reach sequence) in terms of movement initiation, planning, and execution is still not well understood. StartReact (SR) responses triggered by a loud acoustic stimulus (LAS) during the planning and preparation of goal intended actions have been used to probe the state of brainstem neuronal excitability related to posture and movement sequencing (Carlsen, Maslovat, Lam, Chua, & Franks, 2011).

Our preliminary study (Chapter II) (McCombe Waller et al., 2016) demonstrated stroke-related posture and movement planning deficits by showing an abnormal absence of SR responses during the paretic arm reaching movements while standing. In Chapter III, we further investigated whether the deficits are system-wide to both the paretic and nonparetic limbs or are limb-specific by comparing the SR responses during the paretic and nonparetic arm movements. We hypothesize that the motor control of goal-directed reaching while standing following stroke involves abnormal suppression from the cortical level onto the brainstem/spinal circuitry which affects posture and movement planning,

and execution. We also examined the role played by trunk during the APA-reach sequence. Understanding the impairments in the central nervous system process and underlying posture and arm movement limitations allows us to develop mechanism-based neuromodulation therapies such as transcranial direct current stimulation (tDCS) (Floel, 2014). In Chapter IV, we investigated cortical enhancement effects of tDCS on posture and movement planning, initiation, and execution as measured by SR responses in individuals with stroke and healthy controls. Finally, in Chapter V, we provide a summary of the experimental findings, clinical implications, and future direction of this dissertation study.

## 1.2 **Specific aims for Chapter II-IV**

### 1.2.1 Chapter II

*Specific aim:* To investigate the motor preparation and execution of the paretic arm reaching during standing by eliciting a StartReact (SR) response using an LAS in individuals with chronic hemiparesis and healthy age-matched controls.

### 1.2.2 Chapter III

*Specific aim 1:* To examine the posture and movement planning, and execution as measured by the incidence, onset, and magnitude of SR responses in APA-reach sequence in the paretic and nonparetic arms in individuals with chronic hemiparesis and age-matched healthy controls.

*Specific aim 2:* To investigate the APA-reach sequence as measured by spatial and temporal variables of APA-reach sequence in individuals with chronic hemiparesis and age-matched healthy controls.

*Specific aim 3:* To characterize the role played by the trunk in APA-reach sequence as measured by trunk rotation during the paretic and nonparetic arms reaching in standing in individuals with chronic hemiparesis and healthy controls.

### 1.2.3 Chapter IV

*Specific aim:* To determine the modulatory role of the premotor areas (PMAs) including supplementary motor area and premotor cortex in SR responses by 1) applying anodal tDCS over PMAs, which created hyperexcitability, to mimic the pathophysiologic effects of stroke in healthy controls, and by 2) applying cathodal tDCS over PMAs, which normalize excessive excitability, in persons with stroke.

### 1.3 Literature review

This chapter reviews the related literature in: 1) the APA deficits in individuals with stroke, 2) use of an LAS to probe status of motor preparation, 3) PMAs as potential candidate for neuromodulation to improve postural control associated with voluntary arm movement in individuals with stroke, and 4) cortical enhancement effects of transcranial direct current stimulation (tDCS) in individuals with stroke.

#### 1.3.1 Anticipatory postural adjustments in individuals with Stroke

The Central Nervous System utilizes anticipatory postural adjustment (APAs) to counteract the expected mechanical effects of the perturbation arising from the body such as fast arm reaching movement in order to maintain balance (Aruin & Shiratori, 2003). It has been found that the biomechanical effects of the APAs move the center of mass (CoM) upward and forward in order to counteract the initially directed backward and downward reaction force induced by the reaching arm (Bouisset & Zattara, 1987). In addition to stabilize posture by keeping the CoM over the base of support, APAs can also assist in the forthcoming movement dynamics by recreating the angular momentum for effective movement execution especially during rapid arm reaching and transporting arm and trunk to the target when the target is placed beyond arm's length (Kaminski, 2007; Stapley, Pozzo, Cheron, & Grishin, 1999). The typical APA events preceding the voluntary reaching movement involve an early inhibition of soleus or hamstrings muscles, followed by activation of tibialis anterior or quadriceps muscles, driving the center of pressure (CoP) backward. The CoP then moves anteriorly as the trunk and arm moving forward to reach the target. In summary, the APAs act to stabilize the CoM within the base of support to prevent instability, create required angular momentum for

focal movement, and transport arm and trunk to the target (Kaminski, 2007; Stapley et al., 1999).

Studies have found that in individuals with stroke, APAs are usually delayed, disrupted, and decreased (Garland 2003, Garland, 2007; Garland, 2009; Gray, 2012). The biomechanical and neuromuscular abnormalities of APAs in legs and trunk during UE movements are shown in both temporal and spatial aspects in individuals with stroke. Our preliminary study has found that the onset of the APA as measured by the onset of CoP posterior shift is delayed and is it not coordinated with the paretic arm reaching movement onset compared to healthy age-matched controls (McCombe Waller et al., 2016). The magnitude of the APA as measured by the maximal posterior excursion of the CoP in individuals with stroke was smaller compared to healthy subjects. A delay in onset of muscle activation was found not only in leg muscles during the nonparetic arm raising in standing (Garland, Stevenson, & Ivanova, 1997; Horak, Esselman, Anderson, & Lynch, 1984), but also found in trunk muscles during sitting reach movement (Dickstein, Shefi, Marcovitz, & Villa, 2004; Pereira et al., 2013) in comparison with healthy controls. Slijper et al. (2002) using a load drop task found a decrease in the magnitude of the APA as well as inability to modulate the APAs in terms of the amount of muscle activation with the different load drop positions in individuals with stroke (Slijper, Latash, Rao, & Aruin, 2002). Garland et al. (1997) also found less activation and delayed onset in leg muscles during self-initiated rapid arm flexion task in the stroke group compared to the healthy elderly group. The coordination between agonist and antagonist was altered in individuals with stroke as shown by cocontraction and absent triphasic muscle activation pattern in leg muscles in comparison with healthy elderly

subjects (Garland, Gray, & Knorr, 2009). Even in stroke patients who achieved maximum scores in clinical measures (as measured by the Berg Balance Scale and Clinical Outcome Variables Scale), APAs were still significantly impaired, and such impairment negatively affected the quality of life (Garland, Ivanova, & Mochizuki, 2007).

### 1.3.2 Use of a loud acoustic stimulus (LAS) to probe the status of motor preparation

#### 1.3.2.1 *Movement planning and preparation in healthy population*

Loud acoustic stimuli (LAS) can elicit involuntary acts when a person is in a state of preparation for the execution of the upcoming movement (Carlsen, Maslovat, Lam, Chua, & Franks, 2011; Carlsen, Maslovat, & Franks, 2012). The unintentionally released movement has the same spatial and temporal characteristics as the voluntary movement but with very short onset latency (i.e., around 70ms) (Valls-Sole, Rothwell, Goulart, Cossu, & Munoz, 1999). This so-called StartReact (SR) response has been used widely in healthy population to understand how, what, and when movements are planned and prepared. Studies have shown that in a simple reaction time task, when a person is asked to get ready to perform a certain movement after a warning cue and instructed to perform the movement immediately at the go cue, an LAS applied during the preparatory period (ie from the warning cue to the go cue) can trigger a SR (Carlsen, Chua, Inglis, Sanderson, & Franks, 2004; Valls-Sole et al., 1999). The comparable electromyography (EMG) pattern and kinematic characteristic of the triggered movement response with earlier onset latency suggested that the motor program was planned and prepared during the preparatory period and was elicited by an LAS. However, in a choice reaction tasks (i.e., more than one possible movement is required in response to the go signal) or in a

GO/no GO task (i.e., a certain movement is required or not depending on the imperative signal), the presentation of an LAS in addition to the imperative cue did not lead to early response initiation (Carlsen et al., 2008; Carlsen et al., 2009). In addition, when an LAS was applied alone in the absence of motor plan (i.e., in the absence of warning and go cue), the SR response was not triggered (MacKinnon et al., 2007). Combining the above findings, one key feature of the SR response is that it is produced only when a required voluntary act has been instructed in advance without uncertainty. Manipulation of the timing of LAS presentation allows us to know when a given movement is planned and prepared. MacKinnon et al. (2007) showed that the stepping response was progressively assembled between 1400 ms and 100 ms prior to the go. The APA associated with the stepping was elicited with smaller amplitude when an LAS was applied at 1400 ms before the go cue. As an LAS presentation closer to the go cue, the response amplitude became more similar to the normal stepping condition. Similar results were found for wrist extension movements (Carlsen & Mackinnon, 2010), where presenting an LAS as early as 1500 ms in advance of the go cue can elicit the required response in more than 60% of trials and the percentage increased to 90 % when the LAS was applied at 500 ms before the go cue. SR responses has been shown in a variety of movements such as single-joint movements of wrist, elbow (Carlsen et al., 2004; Honeycutt, Kharouta, & Perreault, 2013; Valls-Sole et al., 1999), complex multi-joint movements such as postural responses preceding step initiation (MacKinnon et al., 2007; Rogers et al., 2011), sit-to-stand (Queralt, Valls-Sole, & Castellote, 2008), and obstacle avoidance (Queralt et al., 2008). In addition to LAS, other startling stimuli such as external perturbation can also

act as LAS to trigger a preplanned movement (Campbell, Chua, Inglis, & Carpenter, 2012; Ravichandran, Shemmell, & Perreault, 2009).

### 1.3.2.2 *Movement planning and preparation in individuals with stroke*

Several studies have investigated movement planning and preparation by using SR responses in individuals with stroke. Honeycutt et al. (2012) found that when an LAS replaced the go cue, SR responses in elbow flexion were intact in individuals with stroke as shown by comparable early onset and muscle coordination patterns in comparison with unimpaired subjects, which indicated that stroke subjects are able to plan elbow flexion movements (Honeycutt & Perreault, 2012). The same group also found the SR responses were intact in a hand extension task in individuals with stroke as the onset latency of the SR responses were not different from age-matched controls and the movement trajectories were similar to the trials without the SR responses (Honeycutt, Tresch, & Perreault, 2015). Another study by Marinovic et al. (2016) also found that an LAS can facilitate the paretic arm reaching movement execution in a robotic device while sitting in individuals with stroke when it was presented in conjunction with the go cue (Marinovic, Brauer, Hayward, Carroll, & Riek, 2016).

However, the movement responses triggered by an LAS demonstrated altered muscle activation in individuals with stroke compared to healthy subjects. In the study by Honeycutt et al. (2012), SR responses in elbow extension had altered muscle coordination with inappropriate activity in the flexors possibly resulted from the inability to suppress the classical startle reflex in the paretic arms. A later study by the same group further demonstrated that the task-inappropriate flexor activity increased with UE impairment in subjects post stroke (Honeycutt & Perreault, 2014). Not only the startle reflex interferes

with the SR responses in the UE movements, but also possibly disturbs balance recovery in response to an unexpected postural perturbation, which is served as a startling stimulus same as an LAS in individuals with stroke. A recent study by Celinskis et al. (2018) found that a heightened early bilateral hip flexor activity was seen only in fallers in individuals with stroke.

Combining the results from the above study, it suggested that individuals with stroke may have the ability to plan a single joint movement as shown by similar SR responses compared to the healthy group although the inappropriate activity resulting from the classical startle reflex may interfere with movements. However, in our preliminary study, we (see Chapter II) found that largely absent SR responses during the paretic arm reaching while standing was found in individuals with stroke compared to healthy age-matched controls (McCombe Waller et al., 2016). In this study, an LAS was applied at one of the several time points prior to or at the visual go cue. Individuals with stroke demonstrated a marked reduction in the incidence of SR responses for both reach and anticipatory postural adjustments (APAs) preceding the reach when an LAS was presented before the go cue. Moreover, when the LAS was presented at the go cue, the onsets of APA and reach were delayed in persons after stroke when compared to healthy controls.

### 1.3.2.3 *Distinction between StartReact (SR) responses and classical startle reflexes*

There are several differences between SR responses and classical startle reflexes: the way being triggered, the elicited movement responses, habituation, and whether it can be modulated by pre-pulse inhibition or not.

First, the effect of an LAS depends on the state of movement planning. An SR response is triggered during preparation for the voluntary movement, whereas a classical startle reflex is elicited in the absence of movement plan. The classical startle reflex is a generalized muscle response mainly in flexors that results from an unexpected visual, auditory, somatosensory, or vestibular stimulus to the body with the auditory stimulus being widely and commonly used. The muscle responses usually occur rostral-caudally, starting from eye, neck, upper limb, and then lower limb (Landis, Hunt, & Strauss, 1939). The SR responses are the release of the required movement sequence depending on the task instruction, which is different from the stereotype responses seen in classical startle reflexes. The eyeblink as measured by muscle activation in orbicularis oculi (OOc) has been used widely as an indicator for classical startle reflex (Blumenthal et al., 2005). However, some evidence has shown that OOc activity may not be a valid indicator because the eyeblink reflex is induced more frequently even with low stimulus intensity and it is still activated after habituation (Brown et al., 1991; Rothwell, 2006). Since classical startle reflex also elicits neck flexion which can be detected in muscle activation in sternocleidomastoid muscles (SCM) (Valls-solé, 1999). A better indicator of classical startle reflex would be the activation in SCM. One study by Carlsen et al. (2007) used SCM activity as an indicator to categorize presence or absence of SR responses and found that only trials with SCM activity had very short reaction times and such reaction times were not affected by the intensity effect (Carlsen, Dakin, Chua, & Franks, 2007). Other later studies adopted this strategy to use SCM as an SR response indicator and the findings also suggested that trials with SCM activity had significantly faster onset compared to trials without SCM activation (Honeycutt et al., 2013; Maslovat, Franks, &

Carlsen, 2015). However, there is a possibility that SR responses do occur even without detectable EMG responses in SCM. In studies by Carlsen et al. (2007) and Maslovat et al. (2015), short reaction times were observed in trials without SCM activity despite smaller proportion in comparison with trials with SCM activity. Several studies demonstrated that no differences between trials with and without SCM activity (Campbell, Squair, Chua, Inglis, & Carpenter, 2013; MacKinnon et al., 2007; Rogers et al., 2011). Another difference is that classical startle reflex and SR responses habituate and are modulated in different manners. The classical startle reflex habituates quickly after 2-6 repeated stimuli, whereas an SR response does not (Brown et al., 1991; Valls-Sole, Valldeoriola, Tolosa, & Nobbe, 1997). The other way to modulate the classical startle reflex is using prepulse inhibition (Valls-Sole, Kumru, & Kofler, 2008). When a weak stimulus is applied prior to the LAS, the amplitude of a classical startle reflex is decreased. It has been demonstrated that prepulse inhibition can modulate classical startle reflex but leave SR responses unchanged while the SCM activity was markedly reduced (Valls-Sole, Kofler, Kumru, Castellote, & Sanegre, 2005).

#### 1.3.2.4 *Mechanisms responsible for SR responses*

Two possible mechanisms have been proposed to explain the triggering process of SR responses. One explanation is the brainstem hypothesis, which proposes that SR responses are mediated by a subcortical mechanism without cortical involvement (Valls-Sole et al., 1995; Valls-Sole et al., 1999). It has been hypothesized that the movement sequence is planned and prepared at the cortical level and then stored subcortically. An LAS excites the brainstem regions (pontomedullary reticular formation, PMRF) which also mediate classical startle reflex, resulting in the release of the SR response. This

mechanism was originally based on very short onset latency of SR responses and co-expression of muscle activation seen in classical startle reflex. Since transmission of a sensory signal to auditory cortex takes at least 50-60 ms, the short onset latency (approximately 70 ms) found in Valls-Sole et al. (1999) would make it impossible for cortico-cortical activation including processing sensory signal, making decision, and transmission to spinal motor neurons for motor output (Valls-Sole et al., 1999). Another line of evidence is the co-expression of SCM muscles activation, an indicator of the classical startle reflex. The trials with very short onset latency triggered by an LAS were usually accompanied with muscle activation in SCM muscle, whereas trials without SCM activation had longer onset latency (Carlsen, Chua, Inglis, Sanderson, & Franks, 2009). This suggested that SR responses and classical startle reflexes may be initiated from the same brainstem regions, share at least partial, or have linked pathways. Another mechanism proposed that an LAS acts as a subcortically mediated trigger for a cortically stored motor response in contrast to the brainstem hypothesis. Although there is not enough time for an LAS traveling to auditory cortex via traditional auditory pathway, it is possible that the LAS can trigger movements from cortical areas through a faster subcortical ascending pathway such as reticulo-thalamo-cortical pathway (Koch, Lingenhohl, & Pilz, 1992; Liang, Mouraux, & Iannetti, 2013; Lingenhohl & Friauf, 1994; Samuels & Szabadi, 2008). Some studies demonstrated possible cortical involvement in SR responses by using transcranial magnetic stimulation (TMS) (Alibiglou & MacKinnon, 2012; Stevenson et al., 2014). Based on the premise that the later silent portion of the observed EMG evoked by TMS is associated with cortical inhibition, these two studies demonstrated a significant delay in reaction times of wrist extension triggered

by an LAS when a suprathreshold TMS was applied to the primary motor cortex. These findings suggested that the TMS delayed the SR responses by disruption of the cortical voluntary drive; therefore, the involvement of transcortical pathway is possible.

### 1.3.3 Premotor areas as potential candidates for neuromodulation to improve postural control associated with voluntary arm movement in individuals with stroke

Some studies have demonstrated the role of premotor areas (PMAs) such as supplementary motor area and premotor cortex in postural control both in healthy subjects and stroke patients. In a model proposed by Massion (1992), the supplementary motor area is responsible for selecting appropriate neural networks for anticipatory postural adjustments (APAs) that precede the arm movement, the contralateral primary motor cortex (M1) is responsible for arm movement, and these signals are organized at the subcortical level (Massion, 1992). Recent studies further demonstrated the role of PMAs in postural control. One study by Mihara (2008) suggested that the intention to recover balance is related to enhanced activation in the supplementary motor area as measured by functional Near-infrared spectroscopy in healthy subjects (Mihara, Miyai, Hatakenaka, Kubota, & Sakoda, 2008). In this study, the subjects experienced support surface translation perturbation in different directions with and without a preceding auditory warning cue. By contrast these two conditions (i.e., with and without the preceding auditory warning cue), the perturbation-related activation increased in the supplementary motor area and posterior parietal cortex. The posterior parietal cortex is related to visuospatial attention preparing for the upcoming perturbation and the supplementary motor area is related to preparatory ability including ankle control to recover the balance from the perturbation. Another study by Mihara (2012) demonstrated

that the perturbation-related activation increased in the premotor cortex, supplementary motor area, and the parietal cortex in stroke patients by using the similar experimental design as the previous study by the same research group in 2008 (Mihara et al., 2012). In addition, they also found that the activation in the supplementary motor area was positively related to the balance function as measured by the Berg Balance Scale in the stroke group. Chang et al. (2010) demonstrated that individuals following stroke with premotor cortex lesion had impaired APAs prior to stepping as measured by longer reaction time of the stepping leg and onset latency in tibialis anterior than the healthy and individuals with stroke that spared the premotor cortex (Chang et al., 2010). Another study by Fujimoto (2013) also demonstrated the crucial role of the supplementary motor area in balance recovery post-stroke (Fujimoto et al., 2013). After 4 weeks of intensive rehabilitation, the gain in balance ability as measured by the Berg Balance Scale was positively related to the change in activation of the supplementary motor area.

Another line of evidence further showed the possibility of modulation of PMAs excitability to improve postural control via the projections from PMAs to subcortical level. Recent studies have demonstrated both subcortical and cortical contribution to the generation of anticipatory postural adjustments (APAs). One animal study by Schepens and Drew (2004) showed the contribution of a subcortical pontomedullary reticular formation (PMRF) to the APAs prior to reaching in a cat (Schepens & Drew, 2004). They reported two types of neurons in the PMRF. One type of neuron discharge in relation to the imperative go cue and the other type of neuron discharge in relation to the movement initiation (i.e., reach). The authors proposed that the first kind of neuron is related to the APAs that precede the reaching movement, and the second kind of neuron is related to

the dynamic phase of the reaching movement and postural stabilization that associated with the reaching movement. These signals are proposed to originate from the hierarchically higher center and then convergent in the PMRF (integration site). Since the reticulo-spinal tract regulating postural tone and locomotion arises from the PMRF, and animal studies have shown that large projections (i.e., cortico-reticular axons) from the premotor cortex and supplementary motor area to the PMRF, the possible candidates of the higher centers may include both the premotor cortex and supplementary motor area.

In addition, as mentioned in section B, previous studies showed that the planned movement sequence can be triggered by a loud acoustic stimulus (LAS) with shortened onset latency and unchanged movement characteristics (Valls-Sole et al., 1999). Based on the conduction time and the muscle responses from the eyes and neck resembling the classical startle reflex, it is believed that the PMRF where mediates the startle reflex is the place that also mediates the SR responses representing movement planning and preparation status (Carlsen et al., 2011). A few studies have demonstrated possible cortical modulation onto the subcortical brainstem regions to the process of releasing a planned movement act (Alibiglou & MacKinnon, 2012; Stevenson et al., 2014). One study by Alibiglou and Mackinnon (2012) found that the early released movement triggered by an LAS can be delayed by a suprathreshold TMS over the contralateral primary motor cortex. The suprathreshold TMS altered the descending cortico-reticular pathways and thus delayed the onset latency of the SR response triggered by an LAS. This indicated that the possible modulation from the cortical brain regions to the subcortical PMRF that regulates the SR responses. Given the studies above that showed the potential role of PMAs in balance control, the role of the PMRF in APAs, and the

modulation from PMAs to subcortical PMRF via cortico-reticular pathway, it is possible that PMAs can be new targets for neuromodulation in order to improve postural control associated with reaching movements.

#### 1.3.4 Cortical enhancement effects of transcranial direct current stimulation (tDCS) in individuals with stroke

Transcranial direct current stimulation (tDCS) is a noninvasive electrical stimulation that can be used to modulate the cortical excitability. By application of weak electrical current over the cortex, tDCS can induce changes in resting membrane potentials. Based on the polarity of the electrodes, it can facilitate the cortical activity by using an anodal electrode or inhibit the cortical activity by using a cathodal electrode (Floel, 2014). In post-stroke treatments of deficits, tDCS can be used by two main strategies: either 1) facilitating the lesioned hemisphere by applying an anodal electrode on the lesioned hemisphere or inhibiting the unaffected hemisphere by applying an cathodal electrode on the unaffected hemisphere, or 2) incorporating both approaches with an anodal electrode on the lesioned hemisphere and a cathodal electrode on the unaffected hemisphere (i.e., dual tDCS). Many studies have demonstrated beneficial effects of applying tDCS over M1 on arm, hand, and lower limb motor performance in individuals with stroke (Fregni et al., 2005; Hummel et al., 2005; Madhavan, Weber, & Stinear, 2011; Sohn, Jee, & Kim, 2013; Stagg et al., 2012; Tanaka et al., 2011). In the UE domain, Hummel et al. (2005) showed that anodal tDCS over lesioned M1 in chronic stroke patient improved performance in hand function and cortical excitability (Hummel et al., 2005). Another study by Stagg et al. (2012) showed improvements in response times with the affected hand after anodal tDCS over lesioned M1 and this improvement

was associated with an increase in movement-related cortical activity in the stimulated M1 and functionally interconnected regions including supplementary motor area and premotor cortex, as shown in fMRI (Stagg et al., 2012). Turning to the lower extremity, Madhavan and colleagues demonstrated that improvement in fine motor control of the hemiparetic ankle after training with anodal tDCS applied over the lesioned M1 was significantly larger compared to training with sham tDCS (Madhavan et al., 2011). Another study by Tanaka et al. (2011) demonstrated that anodal tDCS over leg M1 of the lesioned hemisphere enhanced knee extensor force in chronic stroke patients (Tanaka et al., 2011). Furthermore, Sohn and colleagues (2013) showed that after anodal tDCS over leg M1 in the lesioned hemisphere, both isometric strengths of the lesioned quadriceps and static postural stability increased significantly (Sohn et al., 2013). Only two studies examined the effect of tDCS on SR responses in healthy subjects. One study by Nonnekes et al. (2014) stimulated the non-dominant motor region by tDCS and found that following anodal tDCS over the non-dominant motor region, the response onsets of LAS-evoked wrist, ankle movements, and automatic postural responses were earlier compared to the trials without LAS or compared to sham tDCS (Nonnekes et al., 2014). Carlsen et al. (2015) found that anodal tDCS over the supplementary motor area (SMA) led to faster reaction times in a wrist extension task whereas cathodal tDCS resulted in slower reaction times following the stimulation (Carlsen, Eagles, & MacKinnon, 2015). However, no studies were identified that used tDCS over premotor areas (PMAs) as a target for neuromodulation therapies to augment posture and movement planning, and execution following stroke.

## 1.4 References

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## **2 CHAPTER II: IMPAIRED MOTOR PREPARATION AND EXECUTION DURING STANDING REACH IN PEOPLE WITH CHRONIC STROKE<sup>1</sup>**

### **2.1 Abstract**

#### **2.1.1 Objective**

Movement preparation of both anticipatory postural adjustments (APAs) and goal directed movement during a standing reaching task in adults with chronic hemiparesis and healthy controls was investigated.

#### **2.1.2 Methods**

Using a simple reaction time paradigm, while standing on two separate force platforms, subjects received a warning light cue to “get ready to reach” followed by 2.5 s later by an imperative light cue to “reach as quickly as possible” with the paretic arm (matched arm for controls) to touch a target in front of them for a total of 90 trials. In 30 of the reaching trials, a loud acoustic stimulus (LAS) of 123 dB was randomly applied at – 1500, – 1000, – 200, or 0 ms relative to the “go” cue. APA (postural) response were characterized by the onset and maximal posterior displacement of center of pressure (CoP) and onset/offset of electromyography (EMG) from tibialis anterior (TA), soleus (SOL), while reach was characterized by onset and maximal forward displacement of the reach hand and onset of the anterior (AD), biceps brachii (BB) and middle deltoid (MD).

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<sup>1</sup> McCombe Waller, S., Yang, C.-L., Magder, L., Yungher, D., Gray, V. L., & Rogers, M. W. (2016). Impaired motor preparation and execution during standing reach in people with chronic stroke. *Neuroscience Letters*, 630, 38-44. doi: 10.1016/j.neulet.2016.07.010.

### 2.1.3 Results

Subjects with stroke demonstrated a marked reduction in the occurrence of the StartReact responses for both APA and forward reach at all LAS time points indicating movement preparation dysfunction. Movement execution during a cued reach showed significant delays in APA and reach onsets, significant reduction in the magnitude of APA (posterior CoP displacement), and reach excursion, and an increased latency between APA and reach compared to controls. EMG activation patterns for the TA and SOL demonstrated co-contraction compared to the temporally sequenced pattern of control subjects. When the LAS was provided at the “go”, there was earlier but not significant differences in APA onset latency compared to reaching without LAS and significant delays in reach onset latency when compared to control subjects with or without LAS. An early burst of EMG in BB with a further delay of the reach onset compared to reaching without LAS may be indicative of interference of a classical startle reflex activating elbow flexors.

### 2.1.4 Conclusions

Results indicated impairments in movement preparation of both APA's and goal directed upper extremity movement in individuals with stroke, which impact the functional performance of reaching in the standing position.

## 2.2 Introduction

Stroke is the leading cause of long-term disability of daily living skills among adults worldwide (Feigin, Lawes, Bennett, & Anderson, 2003) with common deficits in over 80% of survivors that include postural instability, increase risk of falling, and impairments in reaching and grasping (Broeks, Lankhorst, Rumping, & Prevo, 1999; Hakkennes & Keating, 2005; Weerdesteyn, de Niet, van Duijnhoven, & Geurts, 2008). Numerous studies have underscored the impact of upper extremity (UE) paresis post-stroke on functional outcomes and independence in daily living skills (AHA, 2007; Duncan, 2002a, 2002b; Duncan et al., 1998, 2002; Gowland, deBruin, Basmajian, Plews, & Nurcea, 1992) Few investigations, however, have addressed the additional constraining influence of postural control in standing as a limiting factor in UE function post-stroke.

The motor preparation accompanying forward reaching while standing, normally requires anticipatory postural adjustments (APAs) involving postural muscle activation and associated changes in ground reaction forces (GRFs) and center of pressure (CoP) that contribute to forward reaching and ensure stable standing balance (Massion, 1992; Massion, Alexandrov, & Frolov, 2004). These APAs that precede and the feedforward postural responses that accompany the intended arm movement, normally minimize the destabilizing effects of the impending arm movement and contribute to the forward oriented body movement for reaching. The initiation of goal-directed limb movement has been reported to be delayed until postural adjustments have achieved a level of controlled equilibrium (Massion, 1992; Mille, Simoneau, & Rogers, 2014). Therefore, reaching to grasp an object while standing requires spatial and temporal coordination of multi-joint

actions to effectively integrate the intended arm movement with the postural control needed throughout the task (Kusoffsky, Apel, & Hirschfeld, 2001).

The neuromotor coordination between posture and voluntary movement has been proposed to be organized such that the cortical command for the intended movement might include feedforward signals directed at sub-cortical brainstem structures for generating APAs (Massion, 1992; Massion, Alexandrov, & Frolov, 2004; Drew, Prentice, & Schepens, 2004). This view is supported by studies in quadrupeds showing that the pontomedullary reticular formation is involved in the control of posture through reticulospinal pathways activated by motor corticofugal connections (Drew, Prentice, & Schepens, 2004; Mori, Nakajima, Mori, & Matsuyama, 2004). In human reaction time studies, prepared motor programs can be performed faster with coordination fully intact, when a loud acoustic stimulus (LAS) is applied in advance of or together with the imperative “go” signal, a phenomenon called the StartReact effect. The effect has been attributed to the presence of fully prepared motor programs in subcortical structures and networks, including the pontomedullary reticular formation, that are activated by the LAS without the need for cortical processing of cue-related sensory signals (Carlsen, Chua, Inglis, Sanderson, & Franks, 2004; Valls-Sole, Rothwell, Goulart, Cossu, & Munoz, 1999). Hence, the StartReact response may be used to probe the state of central neuronal excitability during the preparation of both the postural and goal-intended components of a task. For example, during the initiation of stepping, a LAS was delivered at multiple time points prior to an imperative “go” cue to examine motor preparation of the APA-step sequence in healthy individuals and people with Parkinson’s disease (Rogers et al., 2011). It was observed that the planned and prepared APA-step sequence could be triggered by

an LAS as early as 1400 ms prior to the “go” cue. In addition, the coordinated APA-step EMG and kinetic responses were progressively built-up (increased) in duration and amplitude as the expected time of the “go” cue was approached. This demonstrated a progressive modulation in motor excitability for posture and goal intended movement preparation at the brainstem level that was initiated by the LAS trigger.

In performing rapid voluntary arm movements while standing in healthy, APAs are normally characterized by an early inhibition of the soleus (SOL) muscle followed by an activation of the tibialis anterior (TA) that results in an initial posterior displacement of the net COP to accelerate the body center of mass (COM) forward, and then activation of SOL that contributes to decelerating the COM motion (Aruin & Latash, 1995a, 1995b). After stroke, there may be a disruption in the coordination between the APAs and UE movement leading to instability and diminished functional performance. For example, longer latencies and reduced amplitudes in activation of the postural leg muscles during a unilateral nonparetic arm flexion task have been identified (Garland, Stevenson, & Ivanova, 1997; Garland, Willems, Ivanova, & Miller, 2003). Altered muscle activation patterns of the paretic leg have also been seen with paretic arm reaching (Kusoffsky, Apel, & Hirschfeld, 2001)..

While the foregoing information provides insights about the reasons for poor functional performance in reaching activities after stroke, the motor preparation of the APA-reach sequence and the extent to which impaired interactions between postural and goal intended reaching movement contribute to impaired functional performance after stroke remains largely unknown. Limited studies involving stroke patients show intact StartReact responses with similar muscle coordination patterns and timing as unimpaired

participants during a ballistic elbow joint extension movement (Honeycutt & Perreault, 2012), a hand extension task (Honeycutt, Tresch, & Perreault, 2015), and a reaching task (Marinovic, Brauer, Hayward, Carroll, & Riek, 2016) all performed in sitting. However, another report indicated that an unsuppressed classic startle response can interrupt StartReact elbow extension onset times with increasing levels of upper extremity impairment post-stroke (Honeycutt & Perreault, 2014). Taken together, these studies suggest that motor preparation for single isolated joint movements of the UE or gravity minimized reaching movements constrained to a track while seated, may be preserved after stroke but that movement execution may be delayed by heightened CNS excitability. While these studies appear to indicate that motor planning is intact after stroke, the isolated tasks studied while seated may not be representative of motor preparation requirements of the integrated task of antigravity reaching while standing that includes both goal directed movement and postural responses.

To address these issues, our objective was to investigate the motor preparation and execution of paretic arm reaching during standing using an LAS to elicit a StartReact response of the APA-Reach sequence in adults with chronic hemiparesis and healthy age-matched controls. We hypothesized that patients with stroke would have a delayed or diminished StartReact response in both the APAs that precede goal directed reaching in standing as well as the intended reach itself.

## 2.3 **Methods**

### 2.3.1 Participants

Ten participants with hemiplegia due to stroke and five control participants, who were age and sex-matched to 5 of the stroke participants (indicated by asterisk)

participated in the study (Table 1). Inclusion criteria were greater than 6 months post stroke, ability to stand unassisted for 5 minutes, and ability to follow commands. Control participants were neurologically healthy, had no musculoskeletal disorders affecting the lower limbs, and were right-hand dominant by self-report. Written informed consent was obtained before inclusion in the study and procedures were approved by the Institutional Review Board at University of Maryland School of Medicine. The work described in this article was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Table 2.1 Subject Characteristics

Sub #	Age (yrs)	Gender	Type of Stroke and Side	Hand Dom	WMFT	WMFT	FM- UE	Baseline Balance Scores	
					(Time)	(Score)		BERG	ABC
01*	63	M	L Cortical /SCWM	R	68.13	2.30	36	53	90
02	49	M	L Cortical	R	81.33	1.35	18	40	65
03	76	F	R Cortical	R	17.15	2.13	49	37	70
04	41	F	L Cortical/SCWM	R	69.88	1.26	20	30	70
05*	55	M	L Cortical/SCWM	R	72.85	1.61	23	37	50
06*	64	F	L Cortical/SCWM	R	62.25	1.5	22	30	70
07	67	M	R Cortical	R	36.35	2.17	36	40	70
08	61	F	R Cortical /SCWM	R	26.84	2.68	59	40	72
09*	50	F	L Cortical	R	68.32	2.5	38	53	87
10*	55	F	R Cortical	L	64.82	1.48	36	55	90

*SCWM-subcortical white matter; Dom-dominance; BERG- Berg Balance Scale; ABC-Activities Balance Confidence Scale; WMFT-Wolf Motor Function Test; FM-UE- Fugl Meyer \*\*\*Indicates healthy match control subjects*

### 2.3.2 Experimental design and task

A computer-generated analog tone (1 kHz, 40 ms) was used to generate the acoustic stimulus. The tone was amplified and presented by loudspeaker placed 15 cm behind the head of the participant. Peak intensity of the tone near the participant's ears was approximately 123dB. Participants stood on two separate force platforms with their feet placed a natural and comfortable distance apart. An outline of each foot was drawn on the floor to ensure foot placement was the same across trials. A visually cued delayed-response paradigm was used to examine the transition from a stationary standing posture to the rapid initiation of reaching. Task instruction stimuli were presented to the participant using a horizontal bank of LED lights placed at eye level 3 m in front of the participant (Fig 1A). For each trial, a centrally located precue warning stimulus light was presented for 250ms, and was followed 2.5s later by the imperative "go" cue light presented to the right of the warning cue for 250 ms. Participants were instructed to reach for a target ball, located a standardized 5 cm past the outstretched paretic arm of each participant, "as quickly as possible" in response to the "go" cue but not to initiate the

reach before the cue. The 5cm distance was chosen to standardize reach distance past that of a comfortable reach without resulting in a step. Data were inspected on-line for each trial to ensure that the participant did not begin to lean forward after presentation of the precue, which resulted in that trial being discarded and repeated. Participants performed a minimum of 90 reaching trials. In 60 (67%) of the trials no LAS stimulus was applied (cued control trials). In 30 (33%) of the reaching trials, the LAS was applied at one of five time points: -1500, -1000, -500, -200, or 0 ms relative to the "go" cue (Fig 1 B). The LAS trials percentage was to ensure participants did not habituate to the stimulus (Carlsen, Chua, Inglis, Sanderson, & Franks, 2003; Siegmund, Inglis, & Sanderson, 2001). Trials were also collected in which an LAS (5 trials) was delivered between trials while standing without the presentation of a precue instruction or imperative "go" cue, serving as control condition for LAS trials to verify that StartReact responses do not occur in the absence of motor preparation and to confirm the acoustic stimulus could elicit a classic startle response. The order of presentation of cued control and LAS trials was partly randomized with the exception that a LAS trial was not presented during the first five trials and no more than two LAS trials were presented in a row.

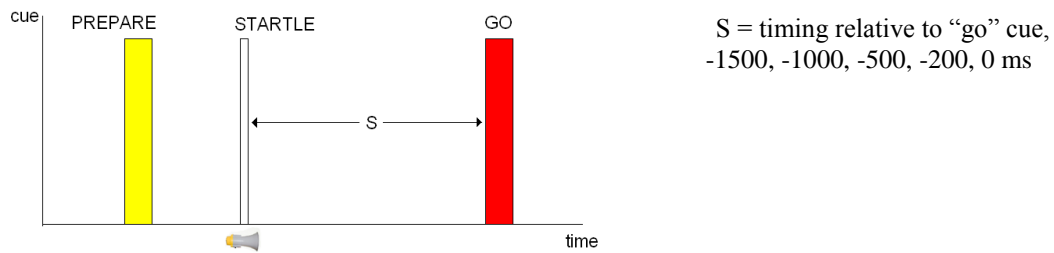
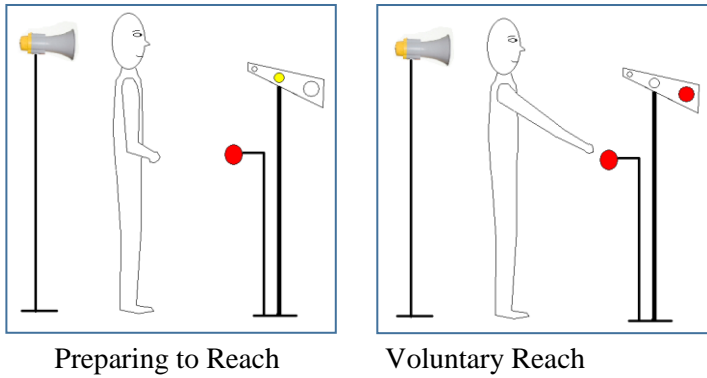


Figure 2.1 Diagram of the presentation of the experimental design. A: Diagram of the presentation of the pre-cue and imperative "go" cue lights and the delivery of the acoustic stimulus. Subjects received a precue to prepare to move by illumination of the center light, followed 2.5 seconds later by the imperative cue to initiate a rapid arm reaching movement. LAS was delivered by a loudspeaker 15 cm behind the head. B: Schematic of the pre-cue ("prepare"), imperative ("go"), and startle ("LAS") cue timing. Control trials had no LAS stimulus. For trials with a LAS, the stimulus was delivered with a relative timing (S) of -1500, -1000, -500, -200, 0 ms relative to the "go" cue.

### 2.3.3 Data collection

Ground reaction forces and moments were collected from two force platforms (AMTI, Watertown, MA) placed beneath the right and left feet. The center of pressure (CoP) beneath each foot and the net CoP were derived from the forces and moments. GRFs were collected at 1 kHz. Electromyographic (EMG) activity of the reaching arm anterior deltoid (AD) and middle deltoid (MD) muscles, bicep brachii (BB), bilateral tibialis anterior (TA), and soleus (SOL) and the sternocleidomastoid muscles were simultaneously detected using surface electrodes (Motion Lab System, Baton Rouge, LA, USA). Following skin preparation, electrodes were placed longitudinally to the muscle fibers at standard recording sites. EMG data were collected at 1500Hz, then bandpass filtered between 25 and 500Hz using a 5<sup>th</sup> order Butterworth filter with the Matlab program filtfilt (MathWorks, Natick, MA). The DC signal bias was removed by subtracting the mean value of the signal from the data. The data was then full-wave rectified. Reflective markers were attached bilaterally over the second metatarsal head, at the estimated joint center locations of the ankles, knees, hips, shoulders, wrists, and at the ear canals and mid-head. Foot markers were included to examine and confirm stepping did not occur as this task was not to include a step. Their locations were recorded for seven seconds per trial at a sampling rate of 120Hz, using a 6-camera Vicon motion analysis system (Vicon, 7388 S. Revere Parkway Suite 901, Centennial, CO 80112).

### 2.3.4 Data analyses

Data analysis was performed using customized software written in MatLab 6.0 (The MathWorks, Natick, MA). Movement preparation was assessed using the presence of StartReact responses relative to the onset of the LAS. To be considered a StartReact

response for the APAs at the -1500, -1000, -500, -200, or 0 time-points relative to the imperative “go” cue, the following criteria needed to be met, 1) EMG burst of the TA, 2) initial posterior displacement of the net COP from both force plates, 3) EMG burst of the SOL muscle all prior to the onset of the voluntary reach, and ,4) for 0 time point only – movement earlier than the voluntary movement. Suppression of the SOL prior to the early TA burst was present in many healthy control trials but was not consistent in individuals with stroke and therefore was not required to indicate a positive StartReact response. The criteria to determine a StartReact response reaching required 1) EMG burst of the AD and /or MD and 2) anterior (forward) movement of the 2<sup>nd</sup> metacarpal head marker, both prior to the onset of the voluntary reach, and, 3) for 0 time point only- movement earlier than the voluntary movement (Carlsen, Maslovat, & Franks, 2012). Movement execution was assessed using the CoP, EMG and reaching kinematics of the cued reach in response to the “go” signal. We intended to use the SCM response as a confirmation of “startle” however in participants with stroke we found tonic SCM activity during this task, possibly secondary to compensatory muscle activation. Given startle responses during control trials with no movement preparation, and the presence of a classic startle in the biceps during reaching movements in our participants with stroke (described in results) we determined the acoustic stimulus was sufficient to elicit a StartReact response. For each trial, onset and offset times of EMG activity in TA, SOL, and AD, MD, BB, onset of the posterior excursion of the CoP, and onset of anterior movement of the 2<sup>nd</sup> metacarpal head marker was identified relative to the "go" or LAS. Onset times of EMG, reach and CoP changes were calculated based on changes of >3 SDs from the mean signal recorded before the "go" or LAS and were verified by visual

inspection. Comparison of the temporal and spatial measures for the StartReact responses for APAs and reach, between the groups, for LAS time points prior to the “Go” were not done as StartReact responses were rarely elicited for participants with stroke for LAS trials provided prior to the “Go” signal (Fig. 2). As an index of response occurrence, we report the incidence of StartReact responses at LAS time periods at 1500, 1000, 500 and 200 ms prior to the imperative” go” for both APA and /or reach responses. For all participants, we did compare the response timing during LAS reaching trials delivered at 0 ms (at the imperative “go”) with control reaching trials without LAS, for StartReact response comparisons similar to previous studies (Honeycutt & Perreault, 2012, 2014; Honeycutt, Tresch, & Perreault, 2015). For the control reaching trials without the LAS, the temporal sequencing of TA and SOL activation (or lag between TA and SOL onset) during reach execution as well as temporal sequencing of APA onset and reach onset (lag) were compared between the groups.

### 2.3.5 Statistical Analyses

Movement execution data were analyzed using a one-way ANOVA to compare both APA and arm movement onsets between the groups. A linear mixed –effect ANOVA was also applied for between-group comparisons between control condition reaching trials (without LAS) and reaching when LAS was presented at the time of the imperative cue. Separate analyses were conducted for each muscle onset latency (TA, AD, MD), CoP onset, and forward reach onset. Tukey Honestly Significant Difference was used for post-hoc comparisons. A significance level of  $p < 0.05$  for all comparisons.

## 2.4 Results

### 2.4.1 StartReact Responses

A StartReact response was seen during 70% of the trials for healthy participants when the LAS occurred prior to the imperative “go” signal, and in only 10% of trials for those with stroke (Table 2). In the stroke group, when LAS was delivered at the time of the “go” cue there was no difference in CoP onset latency (LAS = 245.12 ms  $\pm$ 94.10) compared to reaching without LAS (255.95 ms  $\pm$ 102.93). Furthermore, these onset latencies were significantly delayed when compared to healthy controls with (88.26 ms  $\pm$ .23) and without (143ms  $\pm$ 43) LAS ( $p < 0.01$ ). In the stroke group, presentation of the LAS at the “go” resulted in an earlier activation of AD/MD/BB activity (328 ms $\pm$ 136 (AD); 332 ms $\pm$ 102 (MD); 300ms  $\pm$ 159(BB)), but a further delay of the forward reach onset (501.75 ms $\pm$ 165.21) compared to reaching without LAS (425.66 ms  $\pm$ 171.42;  $p < .01$ ). Control participants demonstrated earlier CoP onsets (88.26 ms  $\pm$ .23;  $p < 0.001$ ) with earlier TA activation (63.10ms $\pm$ .31;  $p < .001$ ) and earlier reach onsets (185.33 ms $\pm$ 65;  $p < 0.005$ ) and AD/MD activation (165.14 $\pm$ 28;  $p < .002$ ) for trials with LAS at the “go” compared to cued reaching without LAS (CoP = 143ms  $\pm$ 43, TA activation =78.33 $\pm$ 32; Reach = 257.75 ms $\pm$ 67.32, AD/MD activation= 178.38 $\pm$ 12) indicating a positive StartReact response with no negative consequences on target accuracy.

Table 2.2: Incidence of StartReact Responses for LAS Trials Prior to “Go”.

Stroke Subject	- 1500	- 1000	- 500	- 200	% StartReact Responses
1	0	0	0	0	0
2	0	0	0	0	0
3	2 <sup>a</sup>	2 <sup>a</sup>	2 <sup>a</sup>	1 <sup>a</sup>	35
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
8	0	1 <sup>a</sup>	2 <sup>a</sup>	0	15
9	0	0	0	0	0
10	2	3	3	3	50
Controls					
1	3	4	3	3	68
2	3	4	3	4	72
3	4	3	4	3	64
4	4	3	4	4	76
5	3	4	4	3	72

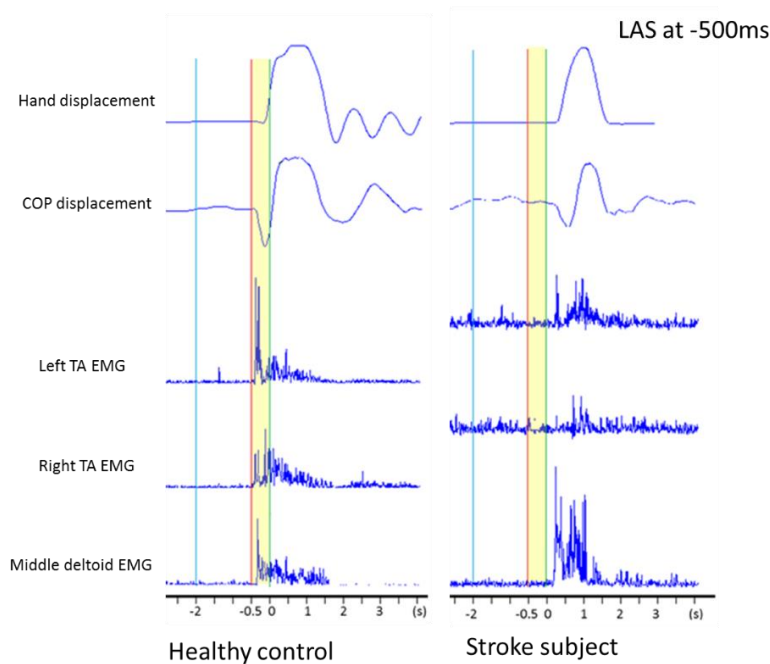


Figure 2.2 Representative examples of single trials when LAS was applied -500ms prior to the imperative “go” cue showing StartReact responses in a healthy subject not present in the stroke subject. The first vertical line indicates the presentation of the warning cue, the second is the LAS and the third line marks the imperative “go” stimulus presentation. Note the StartReact responses can be seen in the highlighted area.

#### 2.4.2 Postural Responses

All participants were able to execute the cued control reaching trials (without LAS) in response to the imperative “go” signal. Those with stroke demonstrated significant delays in these reaching trials ( $p < .002$ ) in CoP onset relative to “go” (255.95 ms  $\pm$ 102.93) compared to healthy controls (143ms  $\pm$ 43.12) as well as significantly reduced ( $p < .002$ ) posterior excursion of the APA (stroke = 1.3 cm $\pm$ 0.46; control = 4.41 cm $\pm$ 1.24).

#### 2.4.3 Reaching Responses

Reach execution was impaired with later reach onset ( $p < .001$ ) as measured by the timing of reach onset (anterior displacement of reach hand marker) (425.66 ms  $\pm$ 171.42;  $p < .001$ ) in stroke participants compared to controls (Reach 257.75 ms $\pm$ 67).

#### 2.4.4 Posture and Reaching Sequencing

Examination of the APA-Reach sequence in individuals with stroke demonstrated a longer temporal lag (170.14 ms  $\pm$ 60.06) between the postural response (TA burst onset) and the reach onset (AD or MD burst onset) compared to healthy controls (100.04 ms $\pm$ 34.00) demonstrating altered coordination between postural and reaching components. EMG data for the controls showed a clear sequencing pattern of muscle activation with timing of the TA burst preceding the SOL burst for all control reaching trials (mean TA onset = 78.33 ms  $\pm$ 32 ; mean SOL onset = 206.43 ms  $\pm$ 84). This pattern was not seen consistently for stroke participants who often showed concurrent activation of the ankle muscles and in some cases reversed activation (mean TA onset = 240.54 ms  $\pm$ 102; mean SOL onset = 268.99 ms  $\pm$ 132).

## 2.5 Discussion

This report investigated the motor planning and execution of paretic arm reaching during standing by using a LAS in adults with chronic hemiparesis and healthy age matched controls. We observed a marked difference in StartReact responses in postural (APA) and goal directed reaching tasks in individuals with stroke compared to healthy controls as well as impaired functional reaching performance. In contrast, healthy controls frequently demonstrated StartReact responses to the LAS when delivered at time points including -1500, -1000, -500, -200, and 0 ms prior to and at the imperative cue. Consistent with previous reports, we observed in healthy adults that coordinated movement sequences, including those involving APAs, can be triggered when a reaction time cue to initiate planned movement is replaced by a startling LAS or is delivered in advance of the expected cue (Alibiglou & MacKinnon, 2012; MacKinnon, et al., 2007). The normally coordinated posture and movement sequence was initiated with reaction times that were considerably shorter than a normal simple voluntary reaction, and can be used to assess movement preparation and planning. Furthermore, the present results also demonstrated a disruption in movement preparation and planning of the APA–reach sequence after stroke. These findings differ from prior reports showing the preservation of StartReact responses in isolated UE upper extremity movements and gravity eliminated reaching performed while seated in individuals with stroke (Honeycutt & Perreault, 2012, 2014; Honeycutt, Tresch, & Perreault, 2015; Marinovic, Brauer, Hayward, Carroll, & Riek, 2016). Compared with single joint movements performed in sitting and reaching with arm constraints, the complexity of the standing reach task may explain these differences between the studies. The present task required the preparation

and planning of both postural balance control and goal directed antigravity reaching as well as their coordination.

The neural networks responsible for APAs have been proposed to be organized subcortically with the timing for executing these responses linked to the cortical command for the voluntary initiation of movement (Massion, 1992; Massion, Alexandrov, & Frolov, 2004). In our participants with cortical and subcortical white matter stroke, we hypothesize that the disruption of movement preparation may have arisen from either a delayed motor cortical command to engage brainstem pathways and/or to abnormal modulation of cortical excitability that negatively influenced (suppressed) activation of brainstem pathways associated with the APA response. Such delays in voluntary movement and StartReact responses have been shown with the use of suprathreshold transcranial magnetic stimulation (Alibiglou & MacKinnon, 2012; Day et al., 1989; Stevenson, Maslovat, Chua, & Franks, 2011). These studies suggest that stimulation of cortical inhibitory pathways can interrupt the cortical drive and delay both StartReact and voluntary movement. In individuals with motor cortical and subcortical lesions due to stroke, other cortical areas such as the supplementary motor area (SMA) show abnormally increased excitability. It is plausible that, given the role of the SMA in the temporal sequencing of multiple movements, abnormal SMA activity may have influenced the ability to elicit StartReact and impacted movement preparation of the postural response in the absence of direct damage to the postural networks (Jurgens, 1984; Tanji, 1994, 1996).

A limitation of the present study was our inability to reliably use the SCM recordings as a marker for startle as has been reported in previous studies of StartReact

after stroke (Honeycutt, Tresch, & Perreault, 2015; Honeycutt & Perreault, 2014). However, it appears that conclusive evidence indicating that the presence of a startle response is either necessary or sufficient for eliciting the StartReact effect is currently lacking (Marinovic, Brauer, Hayward, Carroll, & Riek, 2016).

Finally, while our participants with stroke did not demonstrate StartReact effects involving APA responses when the LAS was delivered at the time of the imperative “go” cue, they did show an earlier BB, AD and MD activation that was accompanied by a further delay in forward movement of the arm when compared to reaching trials without LAS. Several previous studies have identified that cortical damage can lead to a hypermetric classic startle response (Honeycutt & Perreault, 2014; Jankelowitz & Colebatch, 2004) including an unsuppressed startle reflex with task-inappropriate flexor activity during voluntary elbow extension linked with a greater level of impairment. Alternatively, LAS onset shortening at imperative could be due to an intersensory facilitation effect which has been reported by others (Maslovat, Franks, Leguerrier, & Carlsen, 2015; Queralt, Weerdesteyn, van Duijnhoven, Castellote, Valls-Sole, & Duysens, 2008). However, the more general lack of StartReact responses in this study is in contrast with previous studies which have shown similar StartReact responses in individuals with stroke and healthy controls (Honeycutt & Perreault, 2012, 2014; Honeycutt, Tresch, & Perreault, 2015). Our task of reaching while standing is biomechanically more complex than those used in previous studies (Honeycutt & Perreault, 2012, 2014; Honeycutt, Tresch, & Perreault, 2015) and involves the coordination and sequencing of multiple muscles and joints which arguably requires more elaborate preparation and planning. Movement preparation for single joint

movements examined previously (Honeycutt & Perreault, 2012, 2014; Honeycutt, Tresch, & Perreault, 2015) appeared to be preserved in individuals with stroke however, even for these basic motor tasks, deficits were seen that were associated with increased impairment. Considered together, the combined results suggest that impairment alone may not entirely determine deficits in StartReact responses but that task complexity related to postural requirements may also play an important role. Considering the complexity of multi-segmental movements during the performance of daily living skills, our results suggest that motor preparation and planning after stroke may not be as well-preserved as previously reported.

## **2.6 Conclusion**

In this study we have demonstrated impairments in movement preparation of both APAs and goal directed arm movement in individuals with stroke that appeared to disrupt the functional performance of reaching in the standing position. These findings have implications for UE rehabilitation in patients with stroke suggesting that intervention strategies for arm function in standing should include simultaneous postural control challenges to facilitate the coordinated function of the APA-Reach sequence and integration of subcortical postural control and cortically mediated goal directed reaching systems.

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### **3 CHAPTER III: IMPAIRED POSTURE, MOVEMENT PREPARATION, AND EXECUTION DURING BOTH PARETIC AND NONPARETIC REACHING FOLLOWING STROKE**

#### **3.1 Abstract**

Posture and movement planning, preparation, and execution of a goal-directed reaching movement are impaired in individuals with stroke. No studies have shown whether the deficits are generally impaired or are specific to the lesioned hemisphere/ paretic arm. This study utilized StartReact (SR) responses elicited by loud acoustic stimuli (LAS) to investigate the preparation and execution of anticipatory postural adjustments (APAs) and reach movement response during both the paretic and nonparetic arm reaching in individuals with stroke and age-matched healthy controls. Using a simple reaction time paradigm, subjects were asked to get ready to reach after receiving a warning light cue and reach at a “go” light cue. An LAS was delivered at – 500, – 200, 0 relative to the go cue. Kinetic, kinematic, and electromyography (EMG) data were recorded to characterize APA-reach movement response. Individuals with stroke demonstrated system-wide deficits in posture and movement planning, preparation, and execution of APA-reach sequence as shown by significant reduction in the incidence of SR response and impaired APA-reach performance with greater deficits during the paretic arm reaching. Use of trunk compensation strategy as characterized by greater involvement of trunk and pelvic rotation was utilized by individuals with stroke during the paretic arm reaching compared to the nonparetic arm reaching and healthy controls. Our findings have implications for upper extremity (UE) and postural control suggesting that intervention should include not only training for the paretic arm but also for the nonparetic arm with simultaneous

postural control requirements in order to improve the coordination of the APA-reach performance and subsequently reduce instability while performing functional tasks in an upright posture.

### 3.2 Introduction

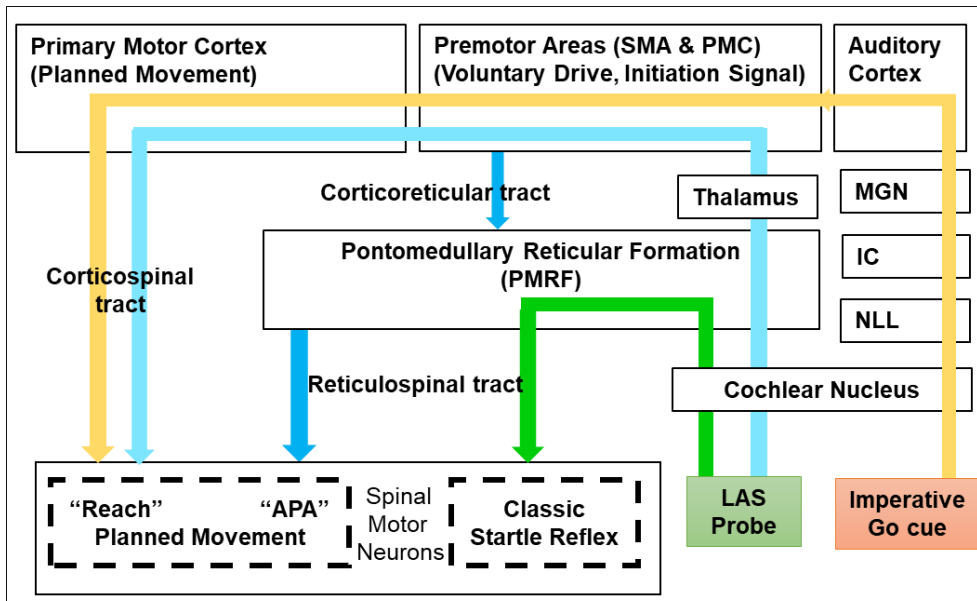
Stroke is the leading cause of long-term disability among adults with approximately 795,000 people having a new or recurrent stroke each year in the USA (Mozaffarian et al., 2016). A majority of stroke survivors have multi-factorial impairments such as limited arm/hand function and impaired postural control in legs and trunk, which lead to difficulty when executing goal-directed reaching movements in standing and subsequently falls (Nakayama et al., 1994; Tyson, Hanley, Chillala, Selley, & Tallis, 2006). The impairments can limit functional recovery, the performance of activities of daily living, and negatively affect the quality of life.

Goal-directed reaching movements while standing involves posture and movement planning, preparation, and execution. A balance perturbation from a voluntary reaching movement normally involves a proactive postural adjustment to counter in advance the movement-related postural disturbance typically referred to as an anticipatory postural adjustment (APA). The typical APA events preceding a voluntary reaching movement are characterized by inhibition of soleus (SOL) activity accompanied by tibialis anterior (TA) burst that moves the center of pressure (CoP) posteriorly, followed by bursts of soleus to move the CoP anteriorly as the hand/arm reaching forward (Stapley et al., 1999). The APAs from legs and trunk are not only responsible for maintaining postural stability, but also provide the dynamic support to improve the

performance of transporting the arm/hand to the target in terms of force or velocity (Kaminski, 2007; Massion, Alexandrov, & Frolov, 2004). Following stroke, disrupted, reduced, delayed APAs in terms of muscle activation patterns in leg muscles, and altered CoP parameters have been commonly reported during nonparetic arm pointing, raising, and load dropping tasks in standing (Garland et al., 1997; Garland et al., 2009; Slijper et al., 2002). Altered trunk muscle activation pattern such as delayed onsets and reduced activity of APAs in the trunk muscles (Dickstein et al., 2004; Pereira et al., 2013), and greater trunk forward displacement (Levin, Mindy Michaelsen, Stella Cirstea, Carmen Roby Bami, Agnès, 2002; Pereira et al., 2013) were also reported in individuals with stroke during sitting reach movement. However, it is not clear how the trunk contributes to the APA-reach sequence in standing in terms of biomechanical characteristics following stroke. Since the APAs that precede and accompany a focal arm movement need to be appropriately directed, timed, and scaled throughout the whole movement, especially in the planning and execution stages (Stapley et al., 1999), the effects of a stroke on these stages of movement need to be determined.

From a mechanistic standpoint, a loud acoustic stimulus (LAS) can be used to probe the state of central neuronal excitability reflecting movement planning and preparation by triggering brainstem mediated posture and movement sequences when delivered prior to a prepared goal-directed action (Alibiglou & MacKinnon, 2012; Valls-Sole et al., 1999). In a simple reaction time paradigm, when the intended action is known in advance, an LAS applied prior to the imperative signal can trigger the prepared movement with earlier onset latency (less than 100ms) but with comparable spatial and temporal kinematics of the voluntary movement sequence (Valls-Sole et al., 1999). This

is so-called a StartReact (SR) response. Based on the short reaction times and the co-expression of classical startle reflex detected by ocular and neck (sternocleidomastoid, SCM) muscles activation, it has been proposed that the pontomedullary reticular formation (PMRF) that mediates the classical startle reflexes is involved in the early release of the prepared movement sequence (Valls-Sole et al., 1999). Studies have found that transcortical pathway may also be involved in the triggering process of SR responses based on the evidence of delaying SR responses by suprathreshold transcranial magnetic stimulation (TMS) over the primary motor cortex (Alibiglou & MacKinnon, 2012) and change of cortical excitability in response to an LAS during movement preparation phase (Marinovic, Tresilian, de Rugy, Sidhu, & Riek, 2014). Base on the literature, our proposed model for the normal release of the planned movement sequence is illustrated in Fig. 3.1.



Adapted from Alibiglou & Mackinnon (2012)

Figure 3.1 The proposed model for the triggering process of a StartReact (SR) response, voluntary movement, and classic startle reflex. The yellow arrow shows the regular pathway for releasing a voluntary movement by a non-startling stimulus. The premotor areas including supplementary motor area (SMA) and premotor cortex (PMC) have input from the go cue via an auditory pathway and auditor cortex. Then the voluntary drive transmits to the primary motor cortex and triggers the release of the planned movement sequence. The blue arrows are the pathways, which an SR response can be released by a loud acoustic stimulus (LAS) via two possible tracts. The premotor areas have input from the LAS and have a voluntary drive that triggers the early release of the planned movement sequence at the level of cortex via the corticospinal pathway or corticoreticulo-spinal pathway. The green arrow represents the known pathway for the release of a classical startle reflex. An LAS travels to the pontomedullary reticular formation (PMRF) and results in a classical startle reflex. Abbreviations: APA: anticipatory postural adjustment. NLL: nuclei of the lateral lemniscus; IC: inferior colliculus; MGN: medial geniculate nucleus.

Limited studies have shown intact SR responses with comparable muscle activation patterns and onset latency during an elbow flexion movement (Honeycutt & Perreault, 2012), a hand extension task (Honeycutt et al., 2015), and a reaching task while sitting with the paretic arm in individuals with stroke compared to healthy controls (Marinovic et al., 2016). However, studies have shown that inappropriate muscle activity resulted from unsuppressed classical startle reflex could interfere with the movement and this effect increased with increasing levels of upper extremity impairment following stroke (Honeycutt & Perreault, 2012; Honeycutt & Perreault, 2014). While these studies suggest the ability of movement planning and preparation for a single joint movement in sitting may be preserved in individuals with stroke, our preliminary study (Chapter II) found that persons after stroke had abnormal posture and movement planning and preparation as shown by an absence of SR responses during rapid paretic arm reaching in standing (McCombe Waller et al., 2016). The demands for posture and task complexity may explain the differences between these studies. However, no studies have shown if the abnormal posture, movement planning and preparation are the system-wide problems in individuals with stroke or if these are specific to the lesioned hemisphere only.

The purpose of this study was to address: 1) posture and movement planning, preparation, and execution as measured by the incidence, onset, and magnitude of SR responses, 2) the APA-reach sequence, and 3) the role played by the trunk in APA-reach sequence as measured by the trunk rotation of the paretic and nonparetic arms reaching in standing in individuals with chronic hemiparesis and healthy controls. Specifically, we aimed to investigate how APA-reach sequence during the nonparetic arm reaching would be different from the paretic reaching and healthy controls. Our hypotheses were as

followings: 1) compared to healthy controls, there would be posture and movement planning and preparation deficits as shown by a reduced incidence, magnitude, and delayed onset of the SR responses in persons after stroke with greater deficits for the paretic arm reaching, 2) compared to healthy controls, impaired APAs-reach sequence would be present in stroke subjects with greater deficits during the paretic arm than the nonparetic arm reaching, 3) compared to healthy controls, increased trunk compensation as shown by greater trunk rotation would be found with more compensation during the paretic arm reaching.

### 3.3 Methods

#### 3.3.1 Participants

Data were collected from 10 individuals with chronic stroke (7 males, 3 females, mean age =  $69.13 \pm 7.61$  yrs, see Table 3.1 for further details) and 10 age-matched healthy controls (6 males, 4 females; mean age =  $66.01 \pm 6.38$  yrs). Inclusion criteria for subjects with stroke were: 1) unilateral cortical or white matter subcortical stroke, 2) age 40 yrs and older, 3)  $\geq 6$  months post ischemic stroke or  $\geq 12$  months post hemorrhagic stroke and completed standard inpatient and outpatient therapy, 4) residual arm hemiparesis as indicated by Fugl-Meyer Upper Extremity (FM-UE) (Gladstone, Danells, & Black, 2002; Sanford, Moreland, Swanson, Stratford, & Gowland, 1993) assessment score between 20-65, 5) have the ability to perform reaching movements with the paretic arm in standing without an assistive device for a minimum of 10 minutes (for participation in testing), and 6) have the cognitive ability to understand, follow verbal instructions, and to give informed consent. Exclusion criteria for subjects with stroke were as followings: 1)

stroke involving bilateral hemisphere, brainstem or cerebellum, and 2) any medical condition precluding participation in testing, such as acute cardiac or respiratory conditions limiting activity and other health conditions significantly affecting balance control and UE movement function beyond the effects of stroke, such as other neurological conditions or peripheral neuropathies. Inclusion criteria for healthy controls are: 1) Age-matched to the stroke subjects and without a history of stroke or any known neurological conditions, and 2) have the cognitive ability to follow two-step commands and to give informed consent. Exclusion criteria for healthy controls were the same as exclusion criteria 2) in stroke subjects. All participants gave informed consent to participate, and the study was approved by the Institutional Review Board at the University of Maryland Baltimore.

### 3.3.2 Experimental design

Each subject participated in 2 sessions: the paretic and nonparetic arms sessions for stroke subjects and the dominant and nondominant arms sessions for healthy controls. Subjects were notified with which arm they are going to reach before each. The order of sessions was randomized. In each session, subjects stood on two separate force platforms with their arms relaxed on the sides and feet placed in a natural and comfortable distance apart. An outline of each foot was drawn on the paper taped to the force platforms to ensure consistent foot placement across trials and between sessions.

### 3.3.3 Loud acoustic stimulus (LAS)

An LAS was used to examine the movement planning and preparation of APAs and goal-directed reaching movement for the paretic and nonparetic arms in stroke subjects and the nondominant and dominant arms in healthy controls while standing. A computer-generated analog tone (1 kHz, 40 ms) was used to create the LAS (Campbell, Chua, Inglis, Carpenter, 2012; Carlsen & Mackinnon, 2010b; Carlsen, Maslovat, Lam, Chua, & Franks, 2011; MacKinnon, Allen, Shiratori, & Rogers, 2013). The tone was amplified and presented by horn speaker (HS-17T, MG Electronics Inc.) placed 30 cm behind the head of the subject. The intensity of the LAS near the subject's ears was approximately 123 dB. Sound intensity was measured with a digital sound meter (Extech 407730, FLIR Commercial Systems Inc.) placed 30 cm from the speaker before each testing to make sure the intensity was consistent for all subjects.

### 3.3.4 Instructed-delayed paradigm

A visually cued delayed-response paradigm was used to examine the transition from a stationary standing posture to the rapid initiation of reaching. Task instruction stimuli were presented to the subject using a horizontal bank of 3 LED lights (left-center-right) placed at eye level 3m in front of the subject. A precue (center) light was presented followed by the imperative "go" cue (left or right) light with an inter-stimulus delay of 2.5 s. The right "go" cue light was illuminated after the precue (center) light when the reach arm was right arm (Fig. 3.2) and the left "go" cue light was illuminated after the precue (center) light when the reach arm was the left arm. The target ball was placed at 65% of subject's height and the target distance was 10cm beyond subjects' maximal

reach distance of the paretic arms for stroke subjects and nondominant arms for healthy controls. In the standing reach task, subjects were instructed to reach for a target ball "as quickly as possible" in response to the "go" cue but not to initiate the reach before the "go" cue.

In each session, subjects performed 65 trials including three conditions. Condition 1, control reach trials (45 trials): these trials consisted of standing reach movements performed with no LAS presented. Condition 2, LAS reach trials (3 time points  $\times$  5 trials, 15 trials): these trials consisted of standing reach movement performed with the LAS presented at one of the 3 time points:  $-500$ ,  $-200$ , or  $0$  ms relative to the "go" cue. These time-points were selected based on past normative studies showing progressive increases in the incidence and magnitude of StartReact responses during this time window reflecting motor preparation (MacKinnon et al., 2007). Condition 3, control LAS trials (5 trials): these trials were collected in which an LAS was delivered during inter-trial standing rest period without reach and without the presence of the precue and go cue, serving as control condition for LAS trials to verify that SR responses did not occur in the absence of movement plan and to confirm that the LAS could elicit a classical startle reflex. The number of trials with LAS (15 LAS trials and 5 control LAS trials) was kept at 33% of all trials to ensure that subjects did not habituate to the stimulus (Carlsen, Chua, Inglis, Sanderson, & Franks, 2003; Siegmund, Inglis, & Sanderson, 2001). The order of presentation of LAS and control reach trials was partly randomized with the exception that the LAS was not presented during the first five trials and no more than two trials with LAS (LAS reach trials and control LAS trials) were presented in a row.

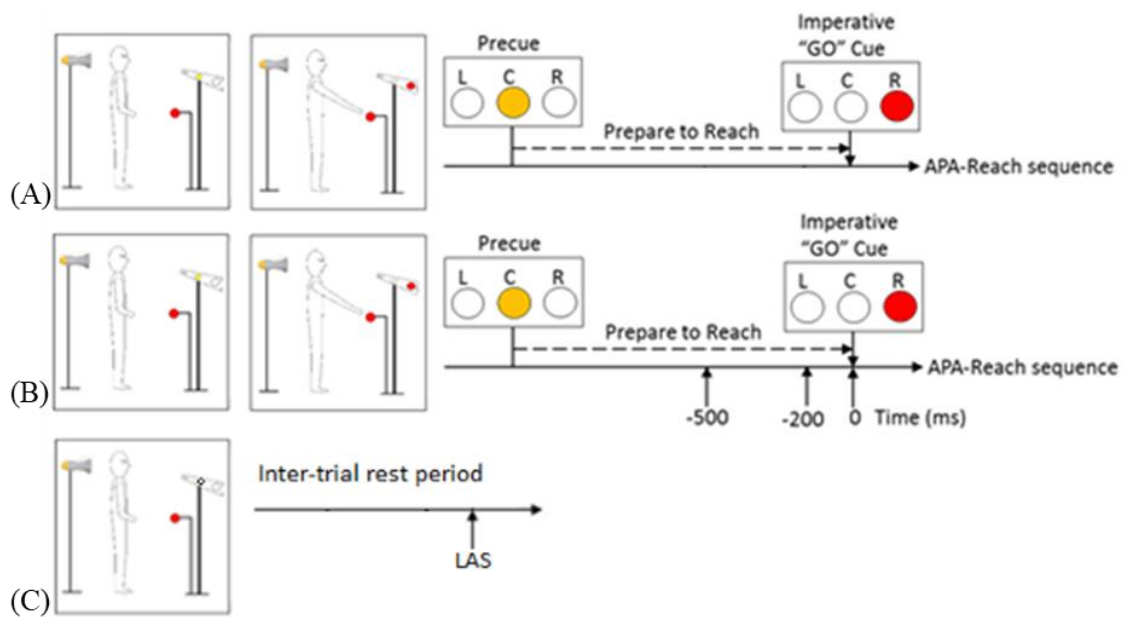


Figure 3.2 Example of a right arm reaching session. (A) a control reach trial, (B) a LAS reach trial, and (C) a control LAS trial.

### 3.4 Data acquisition and analysis

#### 3.4.1 Kinetic recordings

Kinetic data including ground reaction forces and moment were collected from two force platforms (AMTI, Watertown, MA) placed beneath the right and left feet at a collection frequency of 600Hz. These data were filtered with a low-pass, 4<sup>th</sup> order Butterworth digital filter with a cutoff frequency at 10 Hz (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000; Roy et al., 2007). CoP-related parameters were derived from the forces and moments. CoP onset was determined with a threshold equivalent to 5% peak velocity.

#### 3.4.2 Kinematic recordings

Kinematic data were collected at 120 Hz, using a 10-camera Vicon motion analysis system (VICON, Los Angeles, CA). These data were filtered with a low-pass, 4<sup>th</sup> order Butterworth digital filter with a cutoff frequency at 10 Hz. Reflective markers were placed bilaterally on the foot (toe between 2nd and 3rd metatarsal and calcaneus), ankle (lateral malleoli), knee (lateral femoral condyle), shank (in line with medial knee and ankle markers), thigh (in line with greater trochanter of the femur and lateral knee), pelvis (ASIS and sacrum), shoulders (acromion), elbow (lateral epicondyle), upper arm (middle part of the humerus, in line with acromion and lateral elbow), wrist (radius and ulnar styloids), head (glabellum and mastoid process) (Eames, Cosgrove, & Baker, 1999). Kinematic computations of joint centers were performed using a model (Eames et al., 1999) written in commercially available software (BodyBuilder, Vicon, Centennial, CO). Movement onset and offset were determined with a threshold equivalent to 5% peak velocity.

### 3.4.3 Electromyographic (EMG) recordings

The muscle activity was recorded bilaterally from the reaching arm muscle including anterior deltoid (AD), and bilateral leg muscles including tibialis anterior (TA), soleus (SOL), bilateral back muscle (erector spinae at level of L3), and neck muscle with a wireless EMG system TeleMyo™ Direct Transmission System (NORAXON, Scottsdale, AZ) using bipolar surface Ag-AgCl electrodes. Following skin preparation, electrodes were placed longitudinally to the muscle fibers at standard recording sites to minimize skin impedance and maximize signal conduction (Hermens et al., 2000; Roy et al., 2007). All electrodes placements followed the recommendations of SENIAM (Seniam, 2010). Raw EMG signal was sampled at 1500 Hz. The data were bandpass filtered between 30-500 Hz with a 5<sup>th</sup> order Butterworth filter with Matlab program filtfilt, full-wave rectified, and low-pass filtered (10 Hz Butterworth 4<sup>th</sup> order) for smoothing purposes.

### 3.4.4 Data analysis

Kinetic, kinematic, and EMG data were collected for 10 seconds per trial and synchronized through an external trigger. Custom-written Matlab programs (The MathWorks, Inc., Natick, MA) were used to process kinetic, kinematic, and EMG data and all data were verified by visual inspection.

## 3.5 **Outcome variables**

### 3.5.1 Incidence of StartReact (SR) response following LAS

Movement planning and preparation were examined using the presence of SR responses. The incidence of SR responses as an index of response occurrence was

reported during the movement preparation period when the LAS was applied before the “go” cue (i.e. – 500 ms and – 200 ms time points). For the trials where the LAS was presented at the “go” signal, the SR responses were not determined since the responses evoked by the LAS were possibly intermingled with the responses to the imperative “go” signal. To be considered a SR response in the APA or reach, the occurrence of components of APA or reach were required to be met within one of the following time windows: 1) between the LAS and the go cue, or 2) an early onset of < 3 SDs from the average onset in the control reach condition (MacKinnon et al., 2007).

The components for an APA response: 1) an initial posterior shift in the CoP, and 2) an early EMG burst in TA before the onset of reach. In some subjects, a clear suppression of SOL activity was observed. However, this was not consistent in all subjects; therefore, a suppression of SOL activity was not considered as a required component to identify an APA. The components for a reach response: 1) an anterior movement of hand, and 2) an EMG burst in AD or MD.

SR responses were further categorized to full or partial SR APA-reach responses. Full SR APA-reach response required a completed SR response in both APA and reach whereas partial SR APA-reach response required an SR in either APA or reach (see Fig. 3.4).

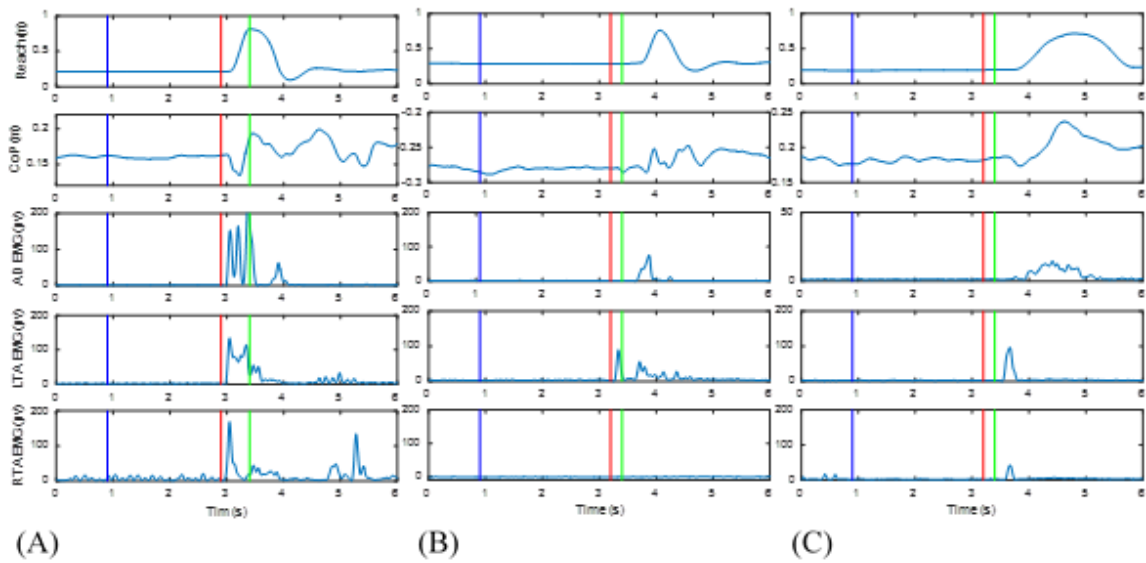


Figure 3.3 Example of a full, partial, and absent SR responses. (A) Full SR response with a completed APA-reach sequence as shown by anterior displacement of hand (top window), posterior CoP displacement (2<sup>nd</sup> window), and corresponding muscle activation (3<sup>rd</sup>-5<sup>th</sup> window) after the LAS before the go cue, (B) partial SR response with SR response only in APA as shown by posterior CoP displacement and TA activation between the LAS and go cue, and (C) absent SR response with neither SR response in APA onset nor SR response in reach. Blue vertical lines represent the timing of the warning cue. Red vertical lines represent the timing of the LAS. Green lines represent the timing of the go cue. Note that in (A) the LAS is at  $-500$  ms relative to the go cue, whereas in (B) and (C) the LAS is at  $-200$  ms relative to the go cue.

### 3.5.2 Reach

1) Reach onset: Reach onsets were determined from the wrist joint center movement in the anterior-posterior direction. For LAS trials, the onset was expressed relative to the timing of LAS. For the control reach condition, the onset was expressed relative to the imperative “go” cue.

2) Peak velocity: Peak velocity was determined as the maximum velocity of the reaching movement defined by the wrist joint center.

### 3.5.3 Anticipatory postural adjustments (APAs)

1) APA onset: Onset of the posterior CoP displacement. For LAS trials, the onset was expressed relative to the timing of LAS. For control reach condition, the onset was expressed relative to the imperative “go” cue.

2) APA magnitude measured by normalized posterior peak CoP displacement: APA magnitudes were determined by the maximum posterior CoP displacements from the onset of the CoP normalized by reach distance.

3) APA peak velocity measured by posterior peak CoP velocity: APA peak velocity was determined as the maximum velocity of the posterior CoP movement.

### 3.5.4 Temporal coordination of APA and reach

1) Lag between APA and reach onsets: Lag was determined from the onset of the APA to the onset of the reach.

### 3.5.5 Trunk contribution during movement execution

1) Trunk rotation: Trunk rotation was determined from the angular displacement of the line connecting both shoulders in the horizontal plane in the direction of the reach at

maximum reach normalized by reach distance. In some trials, an initial angular displacement opposite to the direction of the reach followed by an angular displacement in the direction of the reach was observed. However, the angular displacement opposite to the direction of the reach was not consistent in all subjects and the displacement in the direction of the reach always occurred. It was decided to only analyze the angular displacement “in the direction” of the reach. This strategy was applied to all trunk variables in this section (1-5).

2) Trunk rotation onset: Onset of the trunk rotation.

3) Pelvic rotation: Pelvic rotation was determined from the angular displacement of the line connecting both pelvic joint centers in the horizontal plane in the direction of the reach at maximum reach normalized by reach distance.

4) Pelvic rotation onset: Onset of the pelvic rotation.

5) Trunk-pelvic rotation difference: Trunk-pelvic rotation difference was determined from the difference between horizontal trunk and pelvic angular displacement at maximum reach normalized by reach distance.

### 3.5.6 Muscle activity

1) EMG onset: The onset times of muscle activation was calculated based on changes of  $> 3$  SDs for at least 100 ms from the mean signal recorded before the “go” cue or LAS and a continuous increase of muscle activity was seen. The onset times were verified by visual inspection (Hodges & Bui, 1996). For LAS trials, the onset was expressed relative to the timing of LAS. For control reach condition, the onset was expressed relative to the imperative “go” cue.

### 3.5.7 Clinical outcome measures

1) Fugl-Meyer (FM) assessment: FM was used to confirm eligibility and characterize the level of motor impairment in UE, lower extremity (LE), and sensory impairment in stroke subjects (Gladstone et al., 2002; Sanford et al., 1993). The FM-UE subscale consists of 33 items measuring the movement and reflexes of the shoulder, upper arm, forearm, wrist, hand, and coordination/speed of the arm (range: 0-66). The FM-LE subscale consists of 14 items measuring the movement and reflexes of the hip, knee, ankle, and coordination/speed of the leg (range: 0-34). The sensory subscale consists of 6 items measuring the light touch and position sense of the leg and feet (range: 0-12). The scoring is based on a 3-point scale (0 = cannot perform, 1 = can perform partially, 2 = can perform fully). A higher of FM score represents less motor impairment.

2) Community Balance and Mobility Scale (CB&M) to characterize balance function and mobility in both stroke subjects and healthy controls (Balasubramanian, 2015; Howe, Inness, Venturini, Williams, & Verrier, 2006; Knorr, Brouwer, & Garland, 2010). The CB&M consists of 13 items with a total score of 96 based on a 5-point scale. Each item has specific criteria for scoring with 0, unable to perform to 5, actions are coordinated and controlled without excessive equilibrium reactions. A higher of CB&M score indicates better balance and mobility function.

### 3.6 **Statistical analyses**

A linear mixed-effects model using Group (healthy controls vs. stroke groups), Paretic arm (the paretic arms in the stroke group vs. the nonparetic arms in the stroke group and both arms in healthy controls), LAS condition (LAS at – 500 ms, – 200 ms, 0

ms relative to the go, and control reach) as fixed factors, and subjects as a random factor was performed to test the difference in 1) healthy vs. the nonparetic arm reaching in the stroke group, 2) the paretic vs. nonparetic arm reaching in the stroke group, and 3) healthy controls vs. the paretic arm reaching in the stroke group adjusting for LAS condition. Since the difference between the dominant and nondominant arms is not the main interest of this study, the dominant and nondominant arms were treated as the same in this model. The model included the main effects of Group, Paretic arm, LAS condition, Group  $\times$  LAS condition interaction, Paretic arm  $\times$  LAS condition interaction, and a random intercept for subjects. Interaction term that had the least significant effect was excluded first, then the model was re-examined to see if the remaining interaction term became significant. If the remaining interaction did not reach significance, it would be removed. If the remaining interaction reached significance, it would stay in the model. Stratified analyses were administered when there was an interaction effect to determine any differences of interest. Prior to analysis, proportion variables (e.g., incidence of SR response) were corrected for normality using an arcsine square root transformation. Bonferroni test was used for all post hoc comparisons. Between-group differences in demographic data were tested by independent student t-tests for continuous variables and by chi-squared test for dichotomous variables. All statistical analyses were performed by SPSS v.22 (IBM, Armonk, NY). All statistical tests were made at a significant level of  $p < 0.05$ . All error bars correspond to standard errors.

### 3.7 Results

Table 3.1 presents demographic characteristic in individuals with stroke and age-matched healthy controls. Age and gender were comparable in both groups. The Stroke group had significantly lower scores on CB&M suggesting impaired balance function and mobility compared to healthy controls ( $t_{(18)} = 4.481, p = 0.001$ ). One healthy control (male, age = 81 years old) was excluded from the analysis since the subject's movement data in terms of movement onset time and velocity was deviated markedly from other healthy controls.

Table 3.1 Demographic Characteristic

	Age, y	Gender	Time Poststroke, y	Paresis	Lesion location	Dominant Side	FM-UE (/66)	FM-LE (/34)	CB&M (/96)*
Stroke #1	75.73	M	14.00	R	Cortical & subcortical	R	49	31	58
Stroke #2	63.36	M	5.91	R	Cortical & subcortical	R	39	25	48
Stroke #3	77.63	M	20.51	L	Cortical	L	33	19	30
Stroke #4	62.58	F	7.55	L	Cortical & subcortical	R	30	17	27
Stroke #5	68.14	M	8.81	L	Cortical & subcortical	R	62	26	30
Stroke #6	70.33	F	16.40	R	Subcortical	R	26	21	16
Stroke #7	74.23	F	51.26	L	Subcortical	L	36	19	17
Stroke #8	64.10	M	0.97	R	Subcortical	R	65	34	78
Stroke #9	55.99	M	2.26	R	Subcortical	R	65	34	75
Stroke #10	79.29	M	1.29	L	Subcortical	R	55	29	31
Stroke Mean $\pm$ SD	69.13 $\pm$ 7.61	7M/3F	12.90 $\pm$ 15.00	5R/5L	1 Cortical/5 Subcortical/4 Cortical & subcortical	8R/2L	46.00 $\pm$ 15.06	25.50 $\pm$ 6.36	41.00 $\pm$ 22.61
Controls Mean $\pm$ SD	66.01 $\pm$ 6.38	6M/4F	NA	NA	NA	9R/1L	NA	NA	76.70 $\pm$ 11.11

#### 3.7.1 StartReact (SR) response incidence when the LAS was applied before the “go” cue

Higher incidence of SR responses was seen in most of the healthy controls (66% combining dominant and nondominant arms) whereas in most of the individuals with stroke, there was little or no SR responses (nonparetic vs paretic arm: 38 % vs. 32 %). The incidence of SR response for LAS trials at – 500 ms and – 200 ms for each individual with stroke is presented in Table 3.2.

Comparison among the paretic, nonparetic arms, and healthy controls showed that when the LAS was presented before the go, reduced full SR incidence was found in both

the paretic ( $p = 0.016$ ) and nonparetic arm reaching ( $p = 0.008$ ) in individuals with stroke (Fig 3.4A). There was a trend toward reduced partial SR incidence during the paretic arm reaching compared to the nonparetic arm reaching ( $p = 0.063$ ) in the stroke group and healthy controls ( $p = 0.066$ ) (Fig 3.4B).

Table 3.2 Occurrence and Incidence of Full and Partial StartReact (SR) Responses for LAS Trials Prior to “Go” for Individuals with Stroke

Subject	Paretic Arm						Nonparetic Arm					
	-500 ms		-200 ms		% of SR Response		-500 ms		-200 ms		% of SR Response	
	Full SR	Partial SR	Full SR	Partial SR	Full SR	Partial SR	Full SR	Partial SR	Full SR	Partial SR	Full SR	Partial SR
S#1	3	0	2	1	55 <sup>a</sup>	11 <sup>a</sup>	3	1	2	2	50	30
S#2	0	0	0	2	0	20	1	1	1	4	20	50
S#3	0	0	0	0	0	0	2	1	3	1	50	20
S#4	0	1	1	0	10	10	0	2	0	2	0	40
S#5	0	0	0	0	0	0	0	0	0	0	0	0
S#6	0	0	2	0	20	0	0	0	0	0	0	0
S#7	1	0	0	0	10	0	0	3	0	0	0	30
S#8	2	0	1	1	30	10	0	0	1	1	10	10
S#9	0	3	0	5	0	80	1	0	2	2	30	20
S#10	3	0	4	0	70	0	0	1	0	1	0	20

Note: There were 10 LAS trials (5 trials per time point) for each arm. The percentage of SR response is the percentage of total number of SR response occurrences at – 500 and – 200 ms divided by the total number of trials. <sup>a</sup> There was 1 missing trial due to false start.

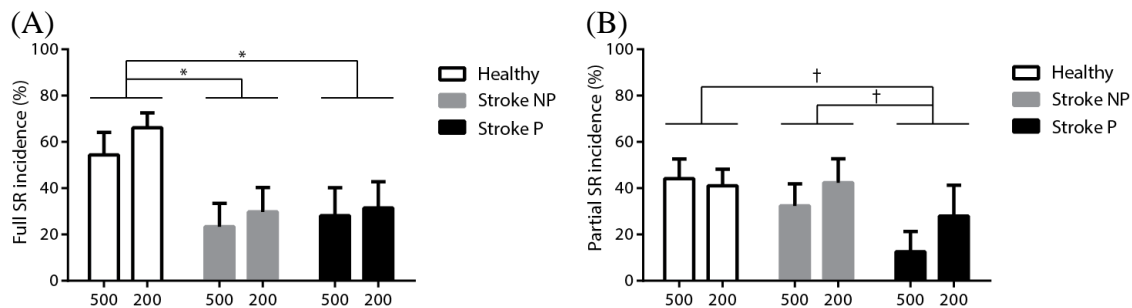


Figure 3.4 Mean ( $\pm$ SE) incidence of (A) full SR response and (B) partial SR response when the LAS was at – 500 and – 200 ms relative to the go in healthy controls, the nonparetic arm (NP) and paretic arm (P) reaching in individuals with stroke. \*  $p < 0.05$  and †  $p < 0.1$ .

### 3.7.2 APA-reach performance

#### 3.7.2.1 *Within the stroke group: the paretic vs. the nonparetic arm*

Greater deficits during the paretic arm reaching were found in later reach onset ( $p = 0.001$ ) (Fig 3.5A), muscle activation onset in AD ( $p < 0.001$ ), longer movement time ( $p < 0.001$ ), and slower reach peak velocity ( $p < 0.001$ ) across all LAS conditions. In terms of APA-reach sequence, no significant difference in lag between APA and reach onsets was found between the paretic and the nonparetic arm reaching (Fig 3.5C). For APA-related variables, although there was no significant difference in APA onsets (Fig 3.5B), later ipsilateral TA onsets was found during the paretic arm reaching at LAS time point – 200 ms and the control reach condition in comparison with the nonparetic arm reaching ( $p = 0.028$ ). During the paretic arm reaching, the APA velocity was faster across all LAS conditions ( $p = 0.015$ ), and APA amplitudes were greater at LAS time point – 500 ( $p < 0.001$ ), – 200 ms ( $p = 0.038$ ), and the control reach condition ( $p < 0.001$ ) in comparison with the nonparetic arm reaching (Fig 3.5D).

#### 3.7.2.2 *Between the stroke and healthy groups*

##### 3.7.2.2.1 *The nonparetic arm vs. healthy controls*

The nonparetic arm also demonstrated altered APA-reach performance compared to healthy controls. During the nonparetic arm reaching, later reach onset ( $p = 0.032$ ) (Fig 3.5A), later muscle activation onset in AD ( $p = 0.043$ ), slower reach peak velocity ( $p = 0.011$ ), and later APA onset ( $p = 0.007$ ) (Fig 3.5B) were observed across all LAS conditions. A later contralateral TA onset was also found during the nonparetic arm reaching compared to healthy controls in the control reach condition ( $p = 0.001$ ).

The effects of the LAS timing were found only in healthy control in the APA amplitude ( $p < 0.001$ ) (Fig 3.5D) and the lag between APA and reach onsets (Fig 3.5C). In healthy controls, the LAS at  $-500$  ms was associated with a smaller APA amplitude and longer lag between APA and reach onsets compared to other conditions. As the stimulation timing closer to the “go” cue, the APA amplitude was gradually increased and the lag was shortened (APA amplitude:  $-500$  ms vs.  $0$  ms:  $p < 0.001$ ;  $-500$  ms vs. control reach:  $p < 0.001$ ;  $-200$  ms vs.  $0$  ms:  $p < 0.001$ ;  $-200$  ms vs. control reach:  $p = 0.001$ ; lag:  $-500$  ms vs.  $-200$  ms:  $p = 0.003$ ;  $-500$  ms vs  $0$  ms:  $p < 0.001$ ;  $-500$  ms vs. control reach:  $p < 0.001$ ;  $-200$  ms vs.  $0$  ms:  $p = 0.001$ ;  $200$  ms vs. control reach:  $p = 0.022$ ).

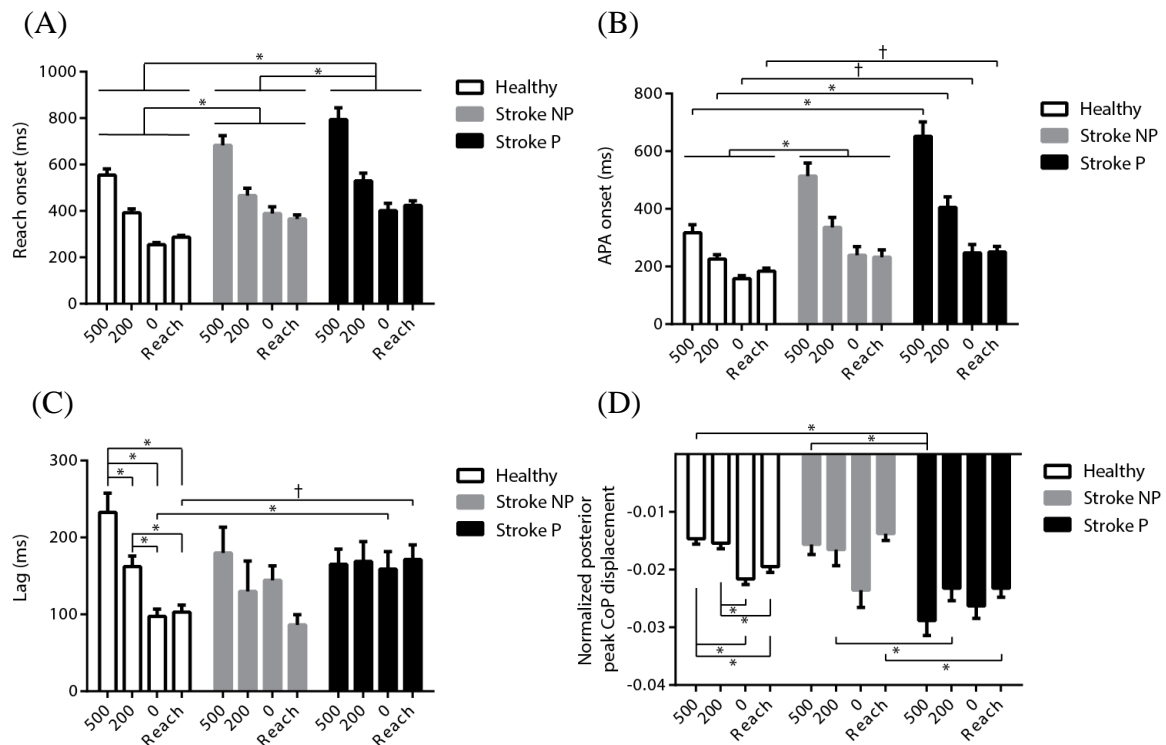


Figure 3.5 Mean ( $\pm$ SE) (A) reach onset, (B) APA onset, (C) lag between APA and reach onsets, and (D) APA amplitude across conditions (LAS at  $-500$ ,  $-200$ ,  $0$  ms relative to the go, and the control reach condition). \*  $p < 0.05$  and †  $p < 0.1$ .

#### 3.7.2.2.2 The paretic arm vs. healthy controls

General impairments in reach performance during the paretic arm reaching compared to healthy controls were reflected in significantly later reach onset ( $p = 0.002$ ) (Fig 3.5A), later muscle activation onset in AD ( $p = 0.002$ ), longer reach movement time ( $-500$  ms:  $p = 0.013$ ;  $-200$  ms:  $p = 0.007$ ;  $0$  ms:  $p = 0.002$ ; control reach:  $p = 0.002$ ), and slower reach peak velocity ( $p < 0.001$ ) across LAS conditions. Temporally uncoordinated APA-reach sequence was found during the paretic arm reaching compared to healthy controls as shown by longer lag between APA and reach onsets when the LAS was at  $0$  ms ( $p = 0.033$ ) and the control reach condition ( $p = 0.063$ ) although the difference in the control reach condition was outside the significance cutoff (Fig 3.5C). For APA-related variables, during the paretic arm reaching, significantly later onsets in APA were observed when the LAS was delivered prior to the go ( $-500$  ms:  $p = 0.002$ ;  $-200$  ms:  $p = 0.001$ ) and a trend toward later onsets were observed when the LAS was at the “go” cue ( $p = 0.089$ ) and the control reach condition ( $p = 0.074$ ) in comparison with healthy controls (Fig. 3.5B). Later ipsilateral and contralateral TA onsets were also found during the paretic arm reaching compared to healthy controls in the control reach condition ( $p = 0.003$  and  $p = 0.013$ ). The APA amplitudes ( $p < 0.001$ ) (Fig 3.5D) and velocity ( $p = 0.029$ ) were greater during the paretic arm reaching compared to healthy controls at LAS time point  $-500$  ms.

### 3.7.3 Trunk performance

#### 3.7.3.1 *The paretic vs. nonparetic arms reaching*

Comparing between the paretic and nonparetic arm reaching, greater trunk rotation ( $p < 0.001$ ) (Fig. 3.6A), earlier trunk rotation onset ( $p < 0.001$ ) (Fig. 3.6B), greater pelvic rotation ( $p < 0.001$ ) (Fig. 3.6C), earlier pelvic rotation onset ( $p < 0.001$ ) (Fig. 3.6D), and reduced trunk-pelvic rotation difference ( $p < 0.001$ ) (Fig. 3.6E) were found during the paretic reaching.

#### 3.7.3.2 *The nonparetic arm reaching vs. healthy controls*

Comparing the nonparetic arm reaching to healthy controls, there were significantly reduced trunk rotation ( $p = 0.038$ ) (Fig 3.6A) and later muscle activation onset in ipsilateral ( $p = 0.007$ ) and contralateral ES ( $p = 0.014$ ) during the nonparetic arm reaching compared to healthy controls. In control reach condition, healthy controls had earlier trunk rotation onset compared to the nonparetic arm reaching in the stroke group ( $p = 0.026$ ) (Fig. 3.6B).

#### 3.7.3.3 *The paretic arm reaching vs. healthy controls*

Greater pelvic rotation ( $p < 0.001$ ) (Fig 3.6C), and reduced trunk-pelvic rotation difference ( $p = 0.004$ ) (Fig 3.6E) were found during the paretic arm reaching compared to the healthy controls. Later muscle activation onsets in ipsilateral ( $p = 0.006$ ) and contralateral ES ( $p = 0.002$ ) were found across all LAS conditions during the paretic arm reaching.

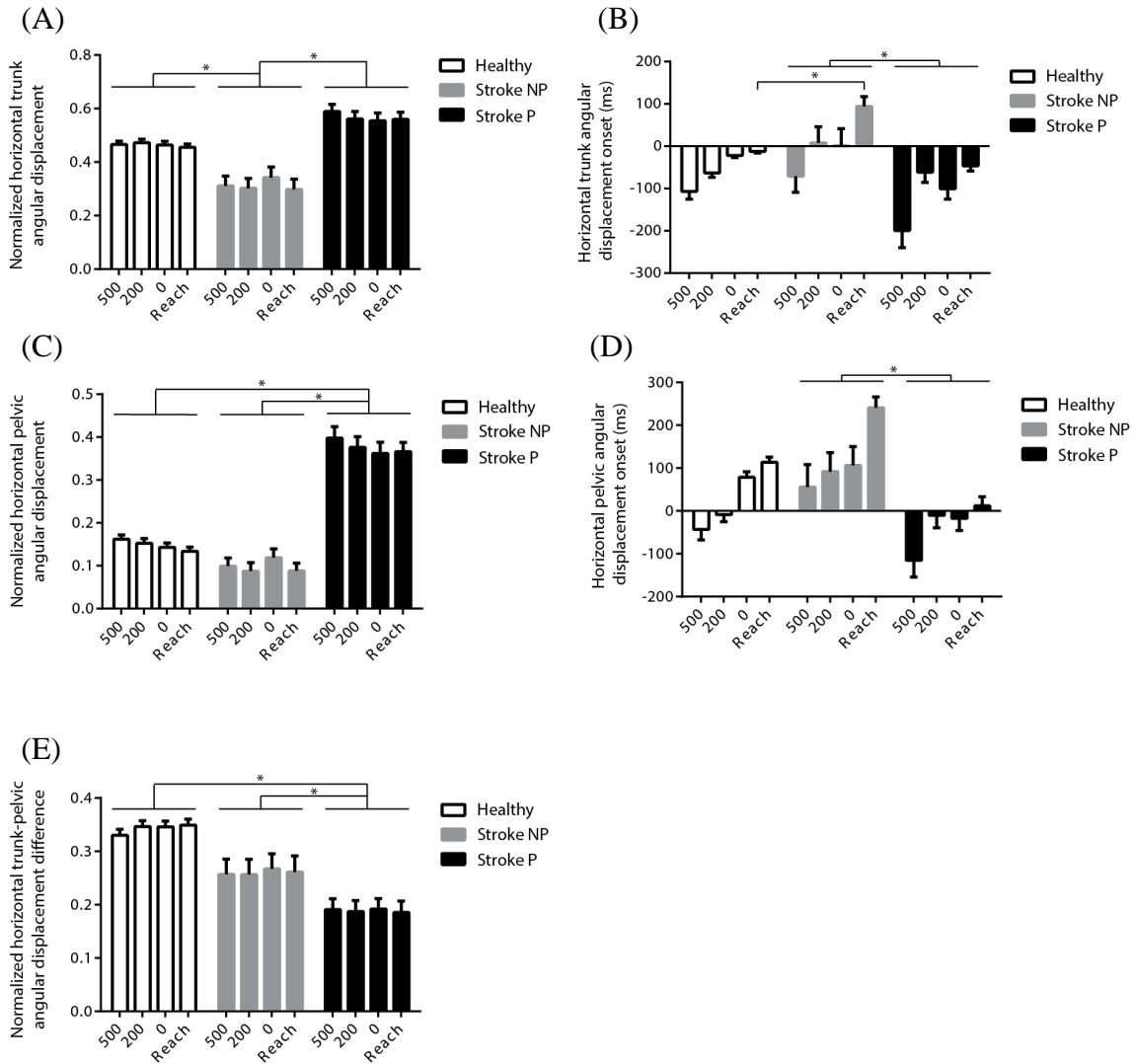


Figure 3.6 Mean ( $\pm$ SE) normalized (A) trunk rotation, (B) trunk rotation onset, (C) pelvic rotation, (D) pelvic rotation onset, and (E) trunk-pelvic rotation difference across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ . Note that trunk and pelvic onsets are presented relative to reach onsets.

### 3.8 Discussion

This study examined posture and movement planning, preparation, and execution during a reaching task while standing in the paretic and nonparetic arms in individuals with stroke and age-matched healthy controls. There are three main findings from this study. First, impaired movement planning and preparation measured by the incidence of SR responses is a general problem in the CNS in persons after stroke, which involves both the lesioned and contralesional side. Second, although individuals with stroke demonstrated better control in APA and reach performance during the nonparetic arm compared to the paretic arm reaching movement, the impairments were still present as shown by later APA, reach onsets, and slower reach velocity in comparison with the healthy controls. Third, individuals with stroke tended to use the “trunk and pelvic” compensatory strategy as shown by earlier trunk and pelvic rotation onset and greater trunk and pelvic rotation in order to transport the paretic arm toward the target.

#### 3.8.1 Abnormal movement planning and preparation in individuals with stroke

SR responses triggered by the LAS have been used widely to reflect the status of movement planning and preparation (Carlsen et al., 2011; Marinovic & Tresilian, 2016). Studies in healthy subjects have shown whether an SR response can be triggered by an LAS depends on if the action is known in advance. This has been demonstrated by that the incidence of SR responses is higher in a simple reaction time task compared to in a choice reaction time task since in the simple reaction task, the required motor action has been pre-instructed and the action can be planned and prepared in advance. This has been also illustrated by the absence of SR responses when the LAS is presented alone without the preparatory and imperative cue (MacKinnon et al., 2007; Valls-Solé et al., 1999).

Another significant factor that can affect the absence or presence of SR responses is the timing of the LAS. Studies have shown that at the early stage of preparatory period, the incidence of SR responses is lower and the incidence of SR responses gradually increases when the LAS timing approaches the imperative cue since the movement is progressively planned and prepared in anticipation of the imperative cue (MacKinnon et al., 2007; MacKinnon et al., 2013). In this study, the incidence of SR responses in the healthy controls was comparable to that of our previous study (McCombe Waller et al., 2016). We did not observe a gradually increase incidence of SR responses as the LAS approached the “go” cue, which may be due to the limitation in our experimental design in which only two LAS time points prior to the “go” (e.g., -500 and -200ms) were used.

In individuals with stroke, as reported in our previous study (McCombe Waller et al., 2016), a mainly absent SR response during the paretic arm reaching was shown when the LAS was presented prior to the “go” signal compared to healthy controls, which indicated impairments in movement planning and preparation of APA-reach sequence. Our current study further demonstrated that the movement planning and preparation ability for a standing reach movement was also impaired when preparing for the nonparetic arm reaching in individuals with stroke, indicating a general issue with movement planning and preparation rather than only specific to the lesioned side. There are two possible reasons for the marked absence of SR responses following stroke: impaired movement planning ability or insufficient movement preparation. The SR responses triggered by LAS serve as an indirect measurement to probe the ability of movement planning and the status of movement preparation by the motor output of a planned and prepared motor action. In this study, we were not able to tease out whether

individuals with stroke had deficits in one or both of those since the absent SR responses following stroke may be due to inability to plan the movement appropriately, insufficient preparation for the upcoming motor action, or both. Future studies may manipulate the motor preparatory activity to tease out if individuals with stroke demonstrate higher incidence of SR responses when they are highly prepared and lower incidence of SR responses when they are not prepared for the motor action. One way to manipulate the motor preparatory activity is by using the anticipation-timing task to provide temporal information about when the motor action is required to be executed. For example, in a study where the subjects were asked to perform a wrist flexion when a clock hand reached to a target, an LAS was presented at 1500, 500, and 150 ms before the time of responding (Carlsen & MacKinnon, 2010). The LAS applied at 150 ms before the time of responding resulted in SR responses in 98% of trials whereas the LAS applied at 1500 and 500 ms before the time of responding resulted in only 0 % and 18 % of SR responses. One can utilize similar paradigm to maximize the motor preparatory activity (i.e., when the clock hand is closed to the target) and examine whether at this stage, stroke subjects still demonstrated marked absence of SR responses. If this is the case, it is possible that the absence of SR responses is due to the inability to plan the movement following stroke.

Two categories of SR responses were elicited during the preparation period when the LAS was presented in advance of the go cue. We separated the responses into two categories based on the completeness of a triggered SR response: full and partial SR responses. Full SR responses (i.e., APA and reach) represented complete movement planning elements while partial SR responses (i.e., SR responses in APA or SR responses

in reach only) represented incomplete movement planning elements for the APA-reach sequence. Although individual differences are observed in each group, generally we find that healthy controls had a higher incidence of full SR responses compared to reduced incidence of SR responses during the paretic and nonparetic arm movements in the stroke group, which suggested that healthy controls had better ability to assemble a “complete” APA-reach sequence. There was no difference in the incidence of full SR between the paretic and the nonparetic movements but there was a trend of higher incidence of partial SR response during the nonparetic arm reaching compared to the paretic arm reaching. This may suggest that when preparing the nonparetic arm movements, the CNS may possibly preserve some degree of movement planning ability although the triggered planned movement was not a complete APA-reach sequence as observed in the partial SR response. Future studies may use multiple time points prior to the “go” and a larger sample size to examine the relevance of full and partial SR responses to motor impairments or functions in individuals with stroke. Altogether, the findings suggest the ability to plan a complete APA-reach sequence was generally impaired and not just specific to the lesioned side in individuals with stroke compared to age-matched healthy controls.

### 3.8.2 Deficits in APA-reach sequence following stroke

In the present study, we found greater APA amplitudes and APA velocity during the paretic arm reaching compared to the nonparetic arm reaching and the healthy controls. The amplitude of APAs is known to be scaled with the movement speed and amplitude in order to counterbalance the postural perturbation from the upcoming arm movement and/or to assist in the reaching performance in healthy subjects (Bouisset,

Richardson, & Zattara, 2000; Horak et al., 1984; Shiratori & Aruin, 2007). In our study, since individuals with stroke performed the reach movements at slower speeds and shorter distance compared to the healthy controls, larger APA amplitudes and velocity were not produced to counteract the perturbations from faster or larger reaching movements. It is plausible that, during forward reaching, larger APA amplitudes as measured by posterior CoP displacement can create a greater moment arm (i.e., the distance between the CoP and center of mass) in order to produce forward angular momentums to assist in moving the body forward to the target (Stapley, Pozzo, & Grishin, 1998). Following stroke, an alternative APA strategy may be used to generate sufficient momentum to compensate the limitations in the paretic arm movement and assist in the forward reaching movement. In terms of the temporal coordination of the APA-reach sequence, there was a trend of longer lag between the onsets of APA and paretic arm reach in the control reach condition and longer lag when the LAS was presented at the “go” compared to healthy controls, indicating altered temporal coordination between postural and goal-directed movement systems. This resembled our previous finding, which demonstrated a longer lag between the onsets of muscle activation for the APA and reach (McCombe Waller et al., 2016).

Consistent with the previous findings, deficits in APA as measured by later APA onset were found during the nonparetic arm reaching movement in standing in individuals with stroke compared to healthy controls, suggesting a postural control issues during the nonparetic arm reaching (Garland et al., 1997; Garland, Willems, Ivanova, & Miller, 2003; V. Gray, Rice, & Garland, 2012). We also observed impairments in the nonparetic arm reach performance as shown by later reach onset and slower reach

velocity, whereas the temporal coordination between the reach and APA onset was not different from that of the healthy controls. Although no studies have demonstrated impaired nonparetic reaching performance in standing following stroke, studies have shown impaired nonparetic arm reaching performance during sitting following stroke according to the theory based on hemispheric specialization for movement control (Mani et al., 2013; Sainburg & Duff, 2006). Specifically, the dominant hemisphere is responsible for predicting limb and task dynamics, whereas the nondominant hemisphere is responsible for specifying limb position through impedance control mechanisms (Mutha, Haaland, & Sainburg, 2012). Therefore, damage in left hemisphere impairs reaching movement trajectory, while damage in the right hemisphere impairs the endpoint control of the reach (Schaefer, Haaland, & Sainburg, 2009). On an inspection of our data, we did not find any specific pattern between dominant versus nondominant side affected stroke nor left versus right hemisphere affected stroke. Thus, it is plausible that the impaired nonparetic arm reaching performance is due to the deficits within the CNS controlling the whole APA-reach sequence given that the temporal coupling of both the APA and reach systems was preserved.

### 3.8.3 A conceptual model for abnormal posture and movement planning and preparation following stroke

It has been proposed that the higher-order premotor areas (PMAs) are responsible for selecting appropriate neural networks for APAs, the contralateral primary motor cortex (M1) is responsible for arm movement, and these signals are organized at the subcortical level (Massion, 1992; Massion et al., 2004). Therefore, the integration of subcortical postural control and cortically mediated goal-directed reaching systems

requires optimal modulation of neuronal excitability between subcortical and cortical levels. We proposed a model for abnormal posture and movement planning and preparation in individuals with chronic stroke (Fig. 3.7A). During movement planning and preparation, normally two primary pathways affect spinal motoneuronal circuitry. One pathway delivers task-related information from PMAs to M1 and subsequently to the spinal cord over the corticospinal pathway. The other cortico-reticulospinal pathway from PMAs to spinal cord via PMRF applies inhibitory modulation in order to prevent premature release and specifies magnitude scaling of the motor action (Cohen, Sherman, Zinger, Perlmutter, & Prut, 2010). Following stroke, PMAs such as premotor cortex or supplementary motor areas show increased excitability (Ward, Brown, Thompson, & Frackowiak, 2003) leading to excessive inhibition via the cortico-reticulospinal pathway, and consequently impairs posture, movement planning, preparation, and execution. This is shown by absent or reduced SR responses and impairments in APA-reach movement performance in the nonparetic arms in our study. However, the temporal coordination between the APA and goal-directed reaching systems is preserved during the nonparetic reaching although both APA and reach onsets were delayed. During the preparation for the paretic arm reaching movement, it is possible that the neuronal networks responsible for the paretic arm movements involves more abnormal inhibition such as increased inhibition from contralesional to ipsilesional M1 (Murase, Duque, Mazzocchio, & Cohen, 2004) (Fig 3.7B). Thus, the neuronal excitability between the cortical and subcortical levels is impaired and subsequently affects the posture, movement planning, preparation, and execution for the paretic arm reaching to a greater extent in comparison with the nonparetic arm reaching. This is shown by generally absent or reduced SR responses,

altered temporal coupling between APA and reach onsets, and more impaired APA-reach performance during the paretic arm reaching in our study in comparison with the nonparetic arm.

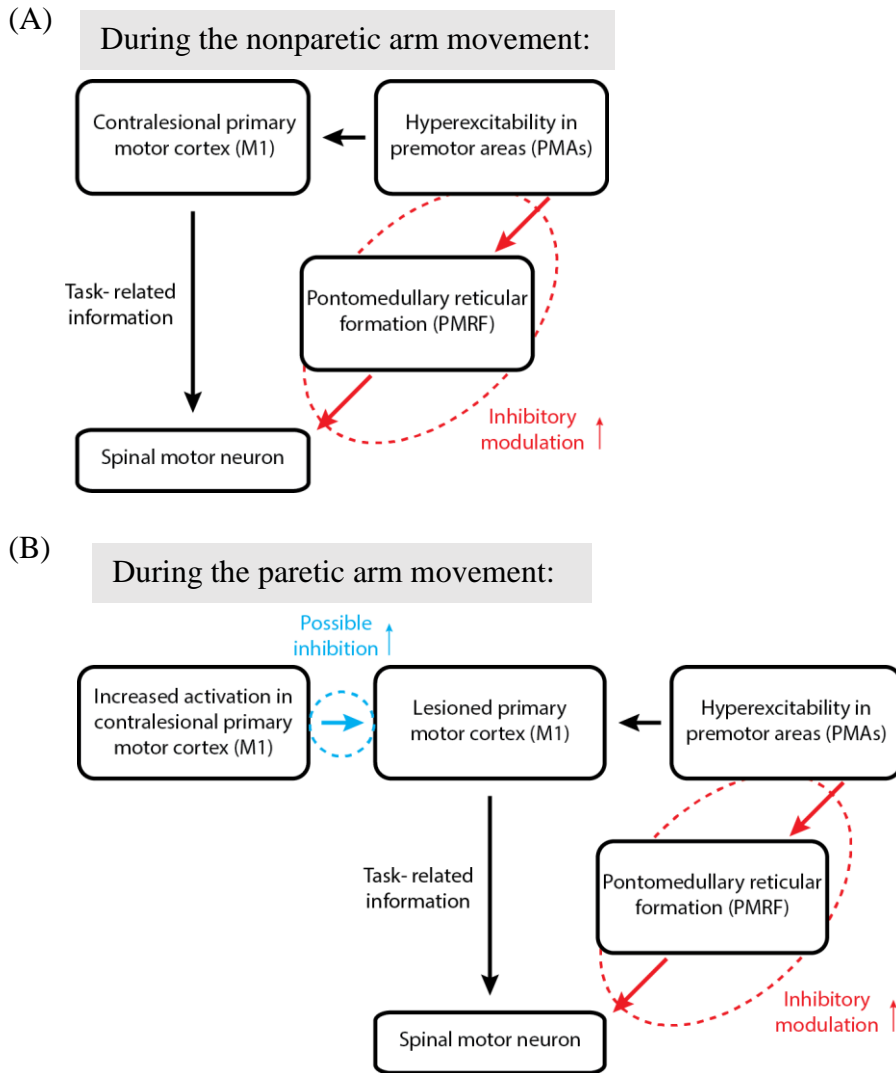


Figure 3.7 This model is adapted from Cohen (2010). The conceptual model for abnormal movement planning and preparation following stroke. During movement planning and preparation, normally two primary pathways affect spinal motoneuronal circuitry. The first pathway delivers task-related information from PMAs to M1 and subsequently to spinal cord over the corticospinal pathway. The second cortico-reticulospinal pathway from PMAs to spinal cord via PMRF applies inhibitory modulation in order to prevent premature release and specify magnitude scaling of the motor action (red). (A) After stroke, hyperexcitability in PMAs leads to excessive inhibitory input via the cortico-reticulospinal pathway (red), and consequently impairs movement planning preparation and performance as shown by absent/reduced StartReact (SR) response during the nonparetic arm reaching. (B) During the paretic arm reaching, there is possible inhibition from increased activation in contralesional primary motor cortex (M1) on the ipsilesional M1 (blue). Thus, movement preparation and performance is impaired to a greater extent compared to during the nonparetic arm reaching movement.

#### 3.8.4 Trunk and pelvic compensation in individuals with stroke

Compensatory strategy as shown by a greater pelvic rotation and reduced trunk-pelvic rotation difference during the reaching movement execution was found in individuals with stroke during the paretic arm reaching compared to the healthy controls. This is consistent with previous studies, which examined the trunk contribution during paretic reaching while sitting (Levin, Michaelson, Cirstea, & Roby-Brami, 2002; Levin, Kleim, & Wolf, 2009). We further demonstrated that stroke subjects utilized “whole body rotation” to compensate for the deficits in elbow extension and shoulder flexion as shown by large pelvic rotation with a small difference between trunk and pelvic rotation during the paretic arm reaching. On the other hand, healthy controls appeared to stabilize at pelvis and utilize mostly trunk rotation while reaching forward to the target. Moreover, with the same target distance, stroke subjects recruited greater and earlier trunk and pelvic rotation during the paretic arm reaching compared to the nonparetic arm reaching. As proposed by Latash and Anson (1996), in individuals with abnormal neuromusculoskeletal systems such as chronic stroke, the central nervous system (CNS) takes into account the changed state of the CNS and peripheral motor system and then chooses a new optimal movement strategy leading to altered or compensatory movement patterns. However, it does not mean that it is impossible for individuals with stroke to demonstrate a relatively normal movement pattern (Latash & Anson, 1996). In fact, many studies have demonstrated that use of “trunk restraint” technique can decrease compensatory trunk strategies and improve reaching while sitting in individuals with stroke (de Oliveira Cacho, Cacho, Ortolan, Cliquet, & Borges, 2015; Pain, Baker, Richardson, & Agur, 2015; Woodbury et al., 2009). Our findings have clinical

implications that the development of therapeutic intervention addressing trunk and pelvic compensation strategy in individuals with stroke during a goal-directed functional task especially in standing is needed.

Although we found reduced trunk rotation during the nonparetic arm reaching in individuals with stroke compared to the healthy controls, this is possibly due to the limitation of the current experimental design in which the target distances were set according to the maximal reach distance of the nondominant arms in healthy controls and the paretic arms in individuals with stroke. Since the maximal reach distance of the paretic arms was shorter, the target distance for the nonparetic arm reaching may be not equally challenging as for the healthy controls. Therefore, the difference in trunk involvement between the healthy controls and the stroke subjects during the nonparetic arm reaching remains unclear. Future studies may examine the trunk contribution between the nonparetic arm reaching in individuals with stroke and healthy subjects by using standardized target distance based on the nonparetic arm reaching ability.

### **3.9 Conclusion**

In summary, the present study showed that posture and movement planning, preparation, and execution of both APAs and goal directed reach were generally impaired in individuals with stroke during not only the paretic but also the nonparetic arm reaching. Specifically, altered APA-reach performance during the nonparetic arm reaching as shown by later APA-reach sequence and slower reach velocity was observed in comparison to the healthy controls. Individuals with stroke utilized excessive use of trunk and pelvic rotation compensation during the paretic reaching. Such difficulties with

planning and executing a complex antigravity reaching arm movement while standing may subsequently lead to loss of balance, limits functional performance during activities of daily living, and negatively impact the quality of life. These findings have implications for UE and postural rehabilitation in individuals with stroke suggesting that in addition to training for the paretic arm, intervention strategies should also include the nonparetic arms training with simultaneous postural control element (e.g., whole-body reaching training) and emphasize on movement speed to facilitate the integration of both cortical-mediated goal-directed reaching and subcortical-mediated postural control systems.

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## **4 CHAPTER IV: EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) ON POSTURE, MOVEMENT PLANNING, AND EXECUTION DURING STANDING VOLUNTARY REACH FOLLOWING STROKE**

### **4.1 Abstract**

#### **4.1.1 Background**

Impaired movement planning and preparation of both anticipatory postural adjustments (APAs) and goal directed movement as shown by a marked reduction in the incidence of StartReact (SR) responses during a standing reaching task was reported in individuals with stroke.

#### **4.1.2 Objective**

We tested how transcranial direct current stimulation (tDCS) applied over the region of premotor areas (PMAs) and primary motor area (M1) affect movement planning and preparation of a standing reaching task in individuals with stroke and healthy subjects.

#### **4.1.3 Methods**

In the healthy subjects, anodal tDCS was used over PMAs to enhance excitability mimicking the pathophysiological effect due to chronic stroke. In individuals with stroke, cathodal tDCS was applied over PMAs to normalize the hyperexcitability. M1 was another stimulation site for anodal tDCS for both groups. Before and after the tDCS, movement planning and preparation of APA-reach sequence was examined by SR responses elicited by a loud acoustic stimulus (LAS). After an instructed delayed period, subjects performed a standing reaching task in response to a “go” light cue. An LAS of

123 dB was randomly delivered at – 500, – 200, and 0 ms relative to the go cue. Kinetic, kinematic, and EMG data were recorded to characterize APA-reach movement response.

#### 4.1.4 Results

Anodal tDCS over M1 led to significant increase of SR incidence at LAS time point – 500 ms in individuals with stroke. Increased trunk involvement during movement execution was found in both groups after anodal M1 stimulation compared to PMAs stimulation. Decreased peak velocity of reaching in healthy subjects was found after anodal M1 stimulation

#### 4.1.5 Conclusions

The findings provide novel evidence that impairments in movement planning and preparation as measured by SR responses for a standing reaching task can be restored in individuals with stroke by the application of anodal tDCS over lesioned M1 but not cathodal tDCS over PMAs.

## 4.2 Introduction

StartReact responses triggered by a loud acoustic stimulus (LAS) during the planning and preparation of goal intended actions have been used to probe the state of brainstem neuronal excitability related to posture and movement sequencing (Carlsen et al., 2011; Carlsen, Maslovat, & Franks, 2012). Abnormal posture and movement planning and preparation as shown by an absence of StartReact responses during standing reaching have been found in our preliminary study (McCombe Waller et al., 2016) and Chapter III. Premotor areas (PMAs) such as supplementary motor areas and premotor cortex are thought to be involved in posture and movement planning (Chang et al., 2010; Viallet, Massion, Massarino, & Khalil, 1992). In preparation for a movement, the neural pathways originating from PMAs to the spinal cord via the reticular formation modulate spinal circuitry through inhibitory effects in order to prevent premature release of the movement (Cohen et al., 2010). Studies of individuals with stroke and healthy subjects also suggested that damage to the premotor cortex following stroke (Chang et al., 2010; Floel, 2014) or temporary inhibition by transcranial magnetic stimulation (TMS) over the supplementary motor areas of healthy subjects (Cohen et al., 2010) impair the anticipatory postural adjustments (APAs) preparation during voluntary stepping. Furthermore, animal studies (Schepens & Drew, 2003; Yakovenko & Drew, 2009) have shown the activation in neurons in subcortical pontomedullary reticular formation (PMRF) were related to the APAs prior to the reaching movement and the signals for the APAs were possibly generated from higher cortical level such as PMAs via cortico-reticular pathway to the PMRF. Our conceptual model (Fig. 4.1) proposed that PMAs normally have a modulatory role in StartReact responses through inhibitory input to

brainstem motor circuits and/or spinal cord via the PMRF. Hence, abnormal hyperexcitability in PMAs due to chronic stroke (Ward et al., 2003) leads to excessive inhibition of the pontomedullary reticular formation (PMRF) and/or spinal cord resulting in an absence of and/or reduced magnitude of SR responses and a disruption of the normal sequencing between posture and movement.

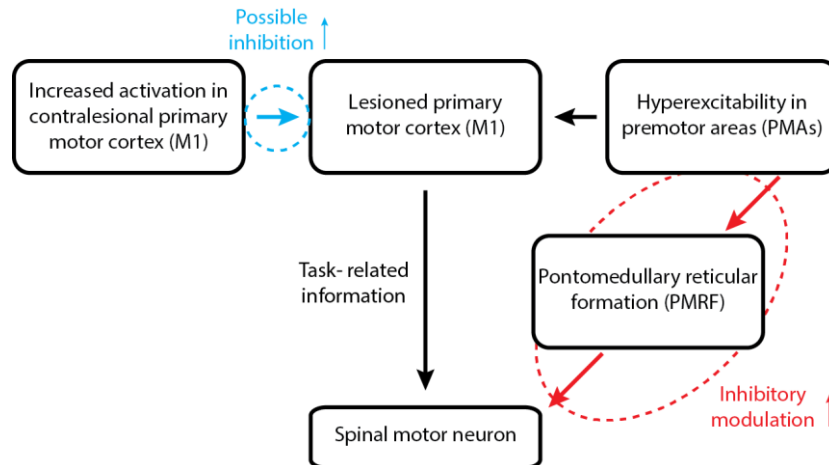


Figure 4.1 This model is adapted from Cohen (2010). The conceptual model for abnormal movement planning and preparation following stroke. During movement planning and preparation, normally two primary pathways affect spinal motoneuronal circuitry. The first pathway delivers task-related information from PMAs to M1 and subsequently to spinal cord over the corticospinal pathway. The second cortico-reticulospinal pathway from PMAs to spinal cord via PMRF applies inhibitory modulation (red) in order to prevent premature release and specify magnitude scaling of the motor action. After stroke, hyperexcitability in PMAs leads to excessive inhibitory input via the cortico-reticulospinal pathway, and consequently impairs movement planning and preparation and performance as shown by absent/reduced StartReact (SR) response. In addition, during the paretic arm reaching, there is possible inhibition from increased activation in contralesional primary motor cortex (M1) on the ipsilesional M1 (blue). Thus, movement planning and preparation and performance is impaired to a greater extent compared to during the nonparetic arm reaching movement.

Cortical excitability can be modulated by the application of weak continuous direct electrical current over a specific location of the head by noninvasive transcranial direct current stimulation (tDCS) (Floel, 2014). Depending on the direct current polarity, tDCS can either up-regulate neuronal excitability, using anodal tDCS or down-regulate it using cathodal tDCS by hyperpolarizing or depolarizing the membrane potentials (Floel, 2014; Nitsche et al., 2003). Many studies have demonstrated beneficial effects of applying tDCS over M1 on arm, hand, and lower limb motor performance in individuals with stroke (Fregni et al., 2005; Hummel et al., 2005; Madhavan et al., 2011; Sohn et al., 2013; Stagg et al., 2012; Tanaka et al., 2011). However, only one recent study demonstrated that StartReact response in ankle dorsiflexion, wrist flexion, and automatic postural responses tasks could be facilitated by applying anodal tDCS over M1 in healthy subjects (Nonnekes, Arroggi et al., 2014). No studies have used tDCS over PMAs as a target for neuromodulation therapy to augment posture and movement planning, preparation, and execution following stroke.

The purpose of this study was to determine the modulatory role of the PMAs (both supplementary motor area and premotor cortex) on StartReact responses following 20 mins of 1) applying anodal tDCS over PMAs in healthy subjects and 2) applying cathodal tDCS over PMAs in persons with stroke. Our hypotheses were as follows: 1) By mimicking the pathophysiologic effects of stroke, anodal tDCS over PMAs, will induce hyperexcitability in healthy subjects, resulting in diminished StartReact responses as measured by reduced incidence, magnitude, and slower onset of the SR responses. 2) Applying cathodal tDCS over PMAs will reduce the neuronal excitability in PMAs thereby helping to improve posture and movement planning and preparation in persons

with stroke, as measured by increased incidence, magnitude, and faster onset of the responses. A secondary purpose was to test the effect of applying anodal, excitatory tDCS over M1 as an alternative stimulation site to enhance the outcomes.

Accomplishment of these aims will provide new insights into the neuromotor control of integrated postural and goal-directed reaching movements, and lead to developing new therapeutic options to normalize the impaired cortico-subcortical circuitry interaction.

### 4.3 Methods

#### 4.3.1 Subject

Data were collected from 10 individuals with chronic stroke (7 males, 3 females, mean age =  $69.13 \pm 7.61$  yrs, see Table 4.1 for further details) and 9 age-matched healthy subjects (6 males, 3 females; mean age =  $66.08 \pm 6.76$  yrs). Inclusion criteria for subjects with stroke were: 1) unilateral cortical or white matter subcortical stroke, 2) age 40 yrs and older, 3)  $\geq 6$  months post ischemic stroke or  $\geq 12$  months post hemorrhagic stroke and completed standard inpatient and outpatient therapy, 4) residual arm hemiparesis as indicated by Fugl-Meyer Upper Extremity (FM-UE) (Gladstone et al., 2002; Sanford et al., 1993) score between 20-65, 5) have the ability to perform reaching movements with the paretic arm in standing without an assistive device for a minimum of 10 minutes (for participation in testing), and 6) have the cognitive ability to understand, follow verbal instructions, and to give informed consent. Exclusion criteria for subjects with stroke were as followings: 1) stroke involving bilateral hemisphere, brainstem or cerebellum, and 2) any medical condition precluding participation in testing, such as acute cardiac or respiratory conditions limiting activity and other health conditions significantly affecting

balance control and UE movement function beyond the effects of stroke, such as other neurological conditions or peripheral neuropathies. Inclusion criteria for healthy subjects are: 1) Age-matched to the stroke subjects and without a history of stroke or any known neurological conditions, and 2) have the cognitive ability to follow two-step commands and to give informed consent. Exclusion criteria for healthy subjects were the same as exclusion criteria 2) in stroke subjects. Participants were also excluded if they did not meet the TMS safety criterion as following: 1) having implantable medical devices including Cardiac pacemaker, spinal cord stimulator, acoustic implant, aneurysm clip, 2) history of seizures, 3) taking medications that reduce cortical excitability that include medications to reduce anxiety, sedatives, and seizure medication, and 4) pregnancy. All participants gave informed consent to participate, and the study was approved by the Institutional Review Board at the University of Maryland Baltimore.

#### 4.3.2 Experimental design

The flow of the experimental design for this study is illustrated in Fig 4.2 and the flow of the experimental procedure for each visit is illustrated in Fig. 4.3 Each subject performed two stimulation sessions (PMAs and M1 stimulation). Healthy subjects performed one experimental condition (anodal tDCS over PMAs) and one control condition (anodal tDCS over M1) sessions. Stroke subjects performed one experimental condition (cathodal tDCS over PMAs) and one control condition (anodal tDCS over M1) sessions. Knowing that PMAs have projections to the M1, the M1 condition was used to validate that PMAs stimulation has additional modulatory effects on the brainstem/spinal circuitry as measured by SR responses. PMAs and M1 stimulation of the lesioned/nondominant hemisphere were applied on two different testing days separated

by at least a 48-hr interval. The order of PMAs and M1 stimulation was randomized for each subject. Each day consists of a pre- and post-tDCS testing in which subjects were instructed to perform a standing reach task in a reaction time paradigm.

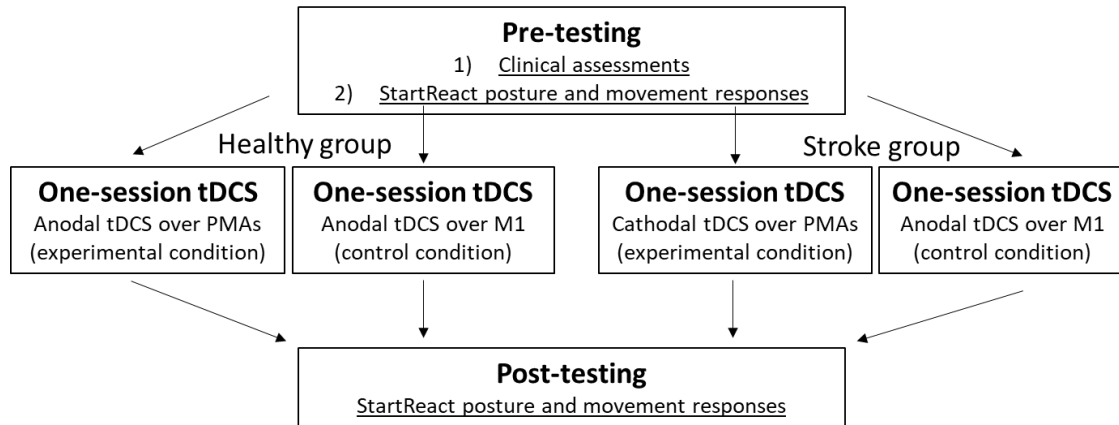


Figure 4.2 Flowchart of the experimental design. tDCS, transcranial direction current stimulation; PMAs, premotor areas; M1, primary motor cortex.

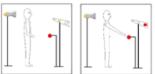

Pre-TMS	Pre-testing	tDCS session	Post-TMS	Post-testing
Hotspots (BB, TA)  MEP (20% MVIC, 120% AMT)	StartReact posture and movement responses 	1 mA, 20 mins	MEP (20% MVIC, 120% AMT)	StartReact posture and movement responses 

Figure 4.3 Flowchart of the experimental procedure for each visit. TMS, transcranial magnetic stimulation; tDCS, transcranial direction current stimulation; BB, biceps brachii; TA, tibialis anterior; MEP, motor-evoked potential; MVIC, maximum voluntary isometric contraction; AMT, active motor threshold.

#### 4.3.3 Transcranial magnetic stimulation (TMS)

Prior to the pre-tDCS testing, motor hotspots for biceps brachii (BB) and tibialis anterior (TA) were located by a single-pulse transcranial magnetic stimulation (TMS) in order to determine the location of tDCS electrodes for PMAs and M1 tDCS stimulation. The hotspot was defined as the optimal stimulation site that has the largest and consistent motor-evoked potential (MEP) at that intensity. We then determined the active motor threshold (AMT) while the subjects exerted a force of 20% maximum voluntary isometric contraction (MVIC) of each muscle. The AMT was defined as the lowest stimulus intensity that could evoke an MEP in 5 out of 10 consecutive trials. A hand-held dynamometer (Chatillon DFX-200 Digital Force Gauge, Itin Scale Co., Inc., Brooklyn, NY) was used to control the level of force exertion. MEPs were measured 10 times at the hotspot for both BB and TA with an intensity of the 120% of active motor threshold at 20% of MVIC. The optimal site for stimulation (hotspot) and the active motor threshold (AMT) were determined according to Rothwell and colleagues (Rothwell et al., 1999). Immediately after the tDCS, changes in cortical excitability as measured by MEPs were assessed again in the same hotspots. A neuronavigation system (Brainsight Version 2, Rogue Research Inc., Montreal, Canada) was used to confirm that the same hotspots were used during TMS testing.

#### 4.3.4 Transcranial direct current stimulation (tDCS)

For PMAs stimulation, in order to cover both supplementary motor area and premotor cortex, the stimulating electrode was placed at the midpoint of the supplementary motor area and premotor cortex (Fig 4.4A). Supplementary motor area was defined as 1.8 cm anterior to the measured location of Cz (Hayduk-Costa,

Drummond, & Carlsen, 2013). Premotor cortex was defined as 2.5 cm anterior to the motor hot spot of the BB (Picard & Strick, 2001). For M1 stimulation that covered both UE and LE representation, the stimulating electrode was placed at the midpoint of UE and LE M1 where TMS elicits twitches in the BB and TA of the limb respectively (Fig. 4.4B). The hotspot of the BB is normally situated approximately 3 cm lateral and 2 cm in front of the Cz (Melgari, Pasqualetti, Pauri, & Rossini, 2008) and the hotspot of the TA is situated approximate 2 cm lateral and 1 cm in front of the Cz (Khaslavskaiia, Ladouceur, & Sinkjaer, 2002). The reference electrode was placed on the forehead above the contralateral orbit. In order to focus the stimulation, we used custom-made tDCS electrodes of 15cm<sup>2</sup> (3 cm × 5 cm). The electrodes, made of carbon-microfiber material, were thoroughly hydrated by saline (0.9% NaCl solution) and secured over the subject's head to assure same electrode placement throughout the study. One-session of tDCS was administered at an amplitude of 1mA for 20 minutes while the subjects were sitting on a chair. After the 20-minute session of tDCS, the subjects performed the post-testing.

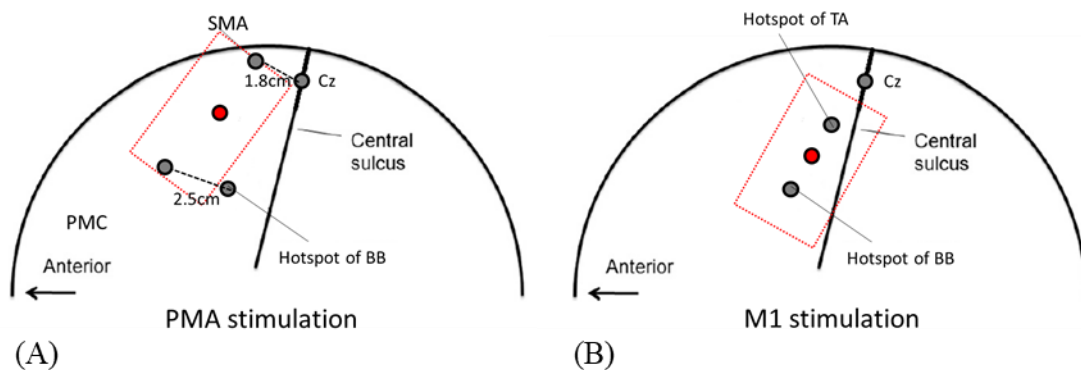


Figure 4.4 Illustration of the stimulation electrode placements for A) PMA stimulation and B) M1 stimulation during tDCS. SMA, supplementary motor area; PMC, premotor cortex.

#### 4.3.5 Instructed-delayed paradigm

A visually cued delayed-response paradigm was used to examine the transition from a stationary standing posture to the rapid initiation of reaching. Task instruction stimuli were presented to the subject using a horizontal bank of 3 LED lights (left-center-right) placed at eye level 3m in front of the subject. A precue (center) light was presented followed by the imperative "go" cue light (left or right) with an inter-stimulus delay of 2.5 s. Subjects were notified with which arm they are going to reach before each session and the reach arm was the same throughout the session. The right "go" cue light was illuminated after the precue (center) light when the reach arm was right arm (Fig. 4.5) and the left "go" cue light was illuminate after the precue (center) light when the reach arm was the left arm. The target ball was placed at 65% of subject's height and the target distance was 10cm beyond subjects' maximal reach distance of the paretic arms for stroke subjects and nondominant arms for healthy subjects. In the standing reach task, subjects were instructed to reach for a target ball "as quickly as possible" in response to the "go" cue but not to initiate the reach before the "go" cue. Stroke subjects reached with the paretic arms and healthy subjects reached with the nondominant arms.

In each session, subjects performed 65 trials including three conditions. Condition 1, control reach trials (45 trials): these trials consisted of standing reach movements performed with no LAS presented. Condition 2, LAS reach trials (3 time points  $\times$  5 trials, 15 trials): these trials consisted of standing reach movement performed with the LAS presented at one of the three time points:  $-500$ ,  $-200$ , or  $0$  ms relative to the "go" cue. These time-points were selected based on past normative studies showing progressive increases in the incidence and magnitude of StartReact responses during this time

window reflecting motor preparation (MacKinnon et al., 2007). In addition, Condition 3, control LAS trials (5 trials): these trials were collected in which an LAS was delivered during inter-trial standing rest period without reach and without the presence of the precue and go cue, serving as catch trials to verify that in the absence of movement plan, an LAS did not elicit SR response. The number of trials with LAS (15 LAS trials and 5 control LAS trials) were kept at 33% of all trials to ensure that subjects did not habituate to the stimulus (Carlsen et al., 2003; Siegmund et al., 2001). The order of presentation of LAS and control reach trials was partly randomized with the exception that the LAS was not presented during the first five trials and no more than two trials with LAS (LAS reach trials and control LAS trials) were presented in a row.

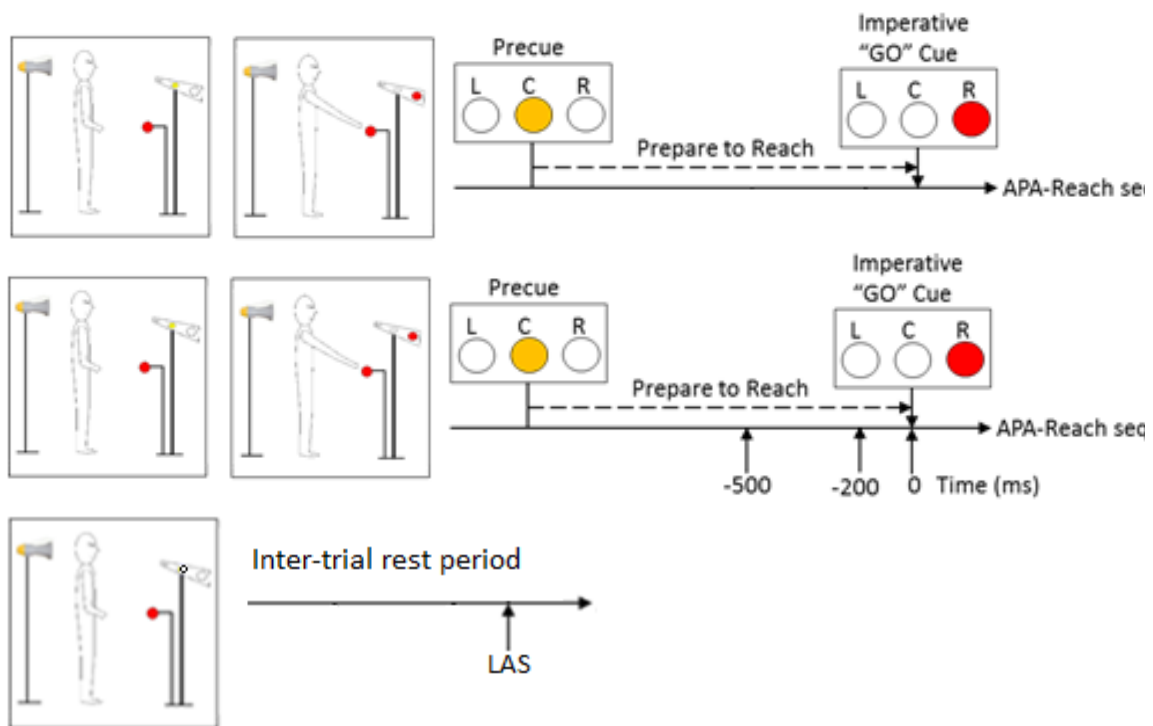


Figure 4.5 Example of a right arm reaching session: (A) a control reach trial, (B) a LAS reach trial, and (C) a control LAS trial.

## 4.4 Data acquisition and analysis

### 4.4.1 TMS and tDCS

TMS stimulation was delivered using a Magstim 200 stimulator (Magstim Company, Dyfed, UK) using a figure-of-eight coil (70-mm standard coil) for BB and a double cone coil (110-mm) for TA. tDCS was applied by an iontophoresor (Chattanooga Ionto, Salt Lake City, Utah). Pre- and Post-tDCS testing procedure were the same as describe in chapter III.

### 4.4.2 Kinetic recordings

Kinetic data including ground reaction forces and moment were collected from two force platforms (AMTI, Watertown, MA) placed beneath the right and left feet at a collection frequency of 600Hz. These data were filtered with a low-pass, 4<sup>th</sup> order Butterworth digital filter with a cutoff frequency at 10 Hz (Hermens et al., 2000; Roy et al., 2007). CoP-related parameters were derived from the forces and moments. CoP onset was determined with a threshold equivalent to 5% peak velocity.

### 4.4.3 Kinematic recordings

Kinematic data were collected at 120 Hz, using a 10-camera Vicon motion analysis system (VICON, Los Angeles, CA). These data were filtered with a low-pass, 4<sup>th</sup> order Butterworth digital filter with a cutoff frequency at 10 Hz. Reflective markers were placed bilaterally on the foot (toe between 2nd and 3rd metatarsal and calcaneus), ankle (lateral malleoli), knee (lateral femoral condyle), shank (in line with medial knee and ankle markers), thigh (in line with greater trochanter of the femur and lateral knee), hip (ASIS and sacrum), shoulders (acromion), elbow (lateral epicondyle), upper arm (middle part of the humerus, in line with acromion and lateral elbow), wrist (radius and ulnar

styloids), head (glabellum and mastoid process) (Eames et al., 1999). Kinematic computations of joint centers were performed using a model (Eames et al., 1999) written in commercially available software (BodyBuilder, Vicon, Centennial, CO). Movement onset and offset were determined with a threshold equivalent to 5% peak velocity.

#### 4.4.4 Electromyographic (EMG) recordings

For MEPs measurement, surface EMG electrodes placed over the biceps brachii (BB) and tibialis anterior (TA) muscles. For pre- and post- tDCS testing, the muscle activity was recorded from the reaching arm muscle including anterior deltoid (AD), medial deltoid (MD), and bilateral leg muscles including tibialis anterior (TA), soleus (SOL), bilateral back muscle (erector spinae at level of L3), and neck muscle (sternocleidomastoid muscle, SCM), with a wireless EMG system TeleMyo™ Direct Transmission System (NORAXON, Scottsdale, AZ) using bipolar Ag-AgCl surface electrodes. Following skin preparation, electrodes were placed longitudinally to the muscle fibers at standard recording sites to minimize skin impedance and maximize signal conduction (Hermens et al., 2000; Roy et al., 2007). All electrodes placements followed the recommendations of SENIAM (Seniam, 2010). Raw EMG signals were sampled at 1500 Hz. The data for the standing reaching task was bandpass filtered between 30-500 Hz with a 5<sup>th</sup> order Butterworth filter with Matlab program filtfilt, full-wave rectified, and low-pass filtered (10 Hz Butterworth 4<sup>th</sup> order) for smoothing purposes.

Kinetic, kinematic, and EMG data for the reaching task were collected for 10 seconds per trial and synchronized through an external trigger. The EMG data for MEP measurement were collected 1 second before and after the TMS. Custom-written Matlab

programs (The MathWorks, Inc., Natick, MA) were used to process kinetic, kinematic, and EMG data and all data were verified by visual inspection.

## 4.5 Outcome variables

### 4.5.1 Incidence of StartReact (SR) response following LAS

#### 4.5.1.1 *SR incidence*

Movement planning and preparation were examined using the presence of SR responses (Fig. 4.6). The incidence of SR responses when the LAS was applied before the “go” cue (i.e., – 500 ms and – 200 ms time points) was reported. The SR responses for the trials when the LAS was presented at the “go” cue were not determined since the responses evoked by the LAS were possibly intermingled with the responses to the imperative “go” signal. To be considered a SR response in the APA or reach, the occurrence of components of APA or reach were required to be met within one of the following time windows: 1) between the LAS and the go cue, or 2) an early onset of < 3 SDs from the average onset in the control reach condition.

The components for an APA response: 1) an initial posterior shift in the CoP, and 2) an early EMG burst in TA before the onset of reach. In some subjects, a clear suppression of SOL activity was observed. However, this was not consistent in all subjects; therefore, a suppression of SOL activity was not considered as a required component to identify an APA. The components for a reach response: 1) an anterior movement of hand, and 2) an EMG burst in AD or MD.

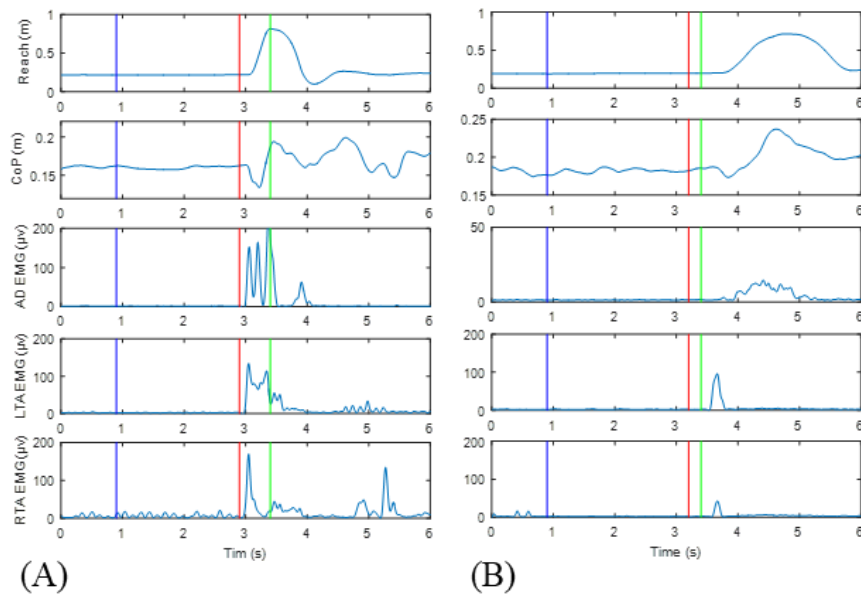


Figure 4.6 Example of a (A) SR response with a completed APA-reach sequence as shown by anterior displacement of hand (top window), posterior CoP displacement (2nd window), and corresponding muscle activation (3rd-5th windows) after the LAS before the go cue and (B) absent response with neither SR response in APA onset nor SR response in reach. Blue vertical lines represent the timing of the warning cue. Red vertical lines represent the timing of the LAS. Green lines represent the timing of the go cue. Note that in (A) the LAS is at  $-500$  ms relative to the go cue, whereas in (B) the LAS is at  $-200$  ms relative to the go cue.

#### 4.5.2 Reach

1) Reach onset: Reach onsets were determined from the wrist joint center movement in the anterior-posterior direction. For LAS trials, the onset was expressed relative to the timing of LAS. For control reach condition, the onset was expressed relative to the imperative “go” cue.

2) Peak velocity: Peak velocity was determined as the maximum velocity of the reaching movement defined by the wrist joint center.

#### 4.5.3 Anticipatory postural adjustments (APAs)

1) APA onset: Onset of the posterior CoP displacement. For LAS trials, the onset was expressed relative to the timing of LAS. For control reach condition, the onset was expressed relative to the imperative “go” cue.

2) APA magnitude measured by normalized posterior peak CoP displacement: APA magnitudes were determined by the maximum posterior CoP displacements from the onset of the CoP normalized by reach distance.

#### 4.5.4 Temporal coordination of APA and reach

1) Lag between APA and reach onsets: Lag was determined from the onset of the APA to the onset of the reach.

#### 4.5.5 Trunk contribution during movement execution

1) Trunk flexion: Trunk flexion was determined by the angular displacement of the line joining the reaching shoulder and the hip joint center on the same side in the sagittal plane at maximum reach normalized by reach distance.

2) Trunk rotation: Trunk rotation was determined from the angular displacement of the line connecting both shoulders in the horizontal plane in the direction of the reach at

maximum reach normalized by reach distance. In some trials, an initial angular displacement opposite to the direction of the reach followed by an angular displacement in the direction of the reach was observed. However, the angular displacement opposite to the direction of the reach was not consistent in all subjects and the displacement in the direction of the reach always occur. We decided to only analyze the angular displacement “in the direction” of the reach.

3) Pelvic rotation: Pelvic rotation was determined from the angular displacement of the line connecting both hip joint centers in the horizontal plane in the direction of the reach at maximum reach normalized by reach distance.

4) Trunk-pelvic rotation difference: Trunk-pelvic rotation difference was determined from the difference between trunk and pelvic angular displacement at maximum reach normalized by reach distance.

#### 4.5.6 Muscle activity

1) EMG onset: The onset times of muscle activation was calculated based on changes of  $> 3$  SDs for at least 100 ms from the mean signal recorded before the “go” cue or LAS and a continuous increase of muscle activity was seen. The onset times were verified by visual inspection (Hodges & Bui, 1996). For LAS trials, the onset was expressed relative to the timing of LAS. For control reach condition, the onset was expressed relative to the imperative “go” cue.

2) EMG magnitude: The muscle activation magnitude was indicated by integrated EMG measured for 75 ms before and after the peak of the EMG burst (150 ms total) (Gray, Ivanova, & Garland, 2012; Gray, Juren, Ivanova, & Garland, 2012).

#### 4.5.7 Neurophysiological measurement

1) Motor-evoked potential (MEP) amplitude: MEP amplitude was measured by the peak-to-peak EMG amplitude elicited by the TMS.

#### 4.5.8 Clinical outcome measures

1) Fugl-Meyer (FM) assessment: FM was used to confirm eligibility and characterize the level of motor impairment in UE, lower extremity (LE), and sensory impairment in stroke subjects (Gladstone et al., 2002; Sanford et al., 1993). The FM-UE subscale consists of 33 items measuring the movement and reflexes of the shoulder, upper arm, forearm, wrist, hand, and coordination/speed of the arm (range: 0-66). The FM-LE subscale consists of 14 items measuring the movement and reflexes of the hip, knee, ankle, and coordination/speed of the leg (range: 0-34). The sensory subscale consists of 6 items measuring the light touch and position sense of the leg and feet (range: 0-12). The scoring is based on a 3-point scale (0 = cannot perform, 1 = can perform partially, 2 = can perform fully). A higher of FM score represents less motor impairment.

2) Community Balance and Mobility Scale (CB&M) to characterize balance function and mobility in both stroke subjects and healthy subjects (Balasubramanian, 2015; Howe et al., 2006; Knorr et al., 2010). The CB&M consists of 13 items with a total score of 96 based on a 5-point scale. Each item has specific criteria for scoring with 0, unable to perform to 5, actions are coordinated and controlled without excessive equilibrium reactions. A higher of CB&M score indicates better balance and mobility function.

#### 4.6 Statistical analysis

A linear mixed-effects model using Stimulation site (PMAs vs. M1) and LAS condition (LAS at – 500 ms, – 200 ms, 0 ms relative to the go, and control reach) as fixed factors, and subjects as a random factor was performed to test the effect of PMAs vs. M1 stimulation adjusting for LAS timing on pre-post change of outcome variables in each group. The model included the main effects of Stimulation site, LAS condition, Stimulation site  $\times$  LAS condition interaction, and a random intercept for subjects. Interaction term that did not reach significance was excluded and the model was re-examined. Stratified analyses were administered when there was an interaction effect to determine any mean differences of interest. Prior to analysis, proportion variables (e.g., incidence of SR response) were corrected for normality using an arcsine square root transformation. Bonferroni adjusted test was used for all post hoc comparison. All outcome variables except for MEP amplitude were transformed and presented as Post – Pre change values. Positive values indicated an increase, whereas negative values indicated a decrease following 20 mins of tDCS. Difference in pre vs. post MEP amplitude in TA and BB was examined by paired t-tests in each group. Between-group differences in demographic data were tested by independent student t-tests for continuous variables and by chi-squared test for dichotomous variables. All statistical analyses were performed by SPSS v.22 (IBM, Armonk, NY). All statistical tests were made at a significant level of  $p < 0.05$ . All error bars correspond to standard errors.

## 4.7 Results

Table 4.1 presents demographic characteristic in individuals with stroke and age-matched healthy subjects. Age and gender were comparable in both groups. The stroke group had significantly lower scores on CB&M suggesting impaired balance function and mobility compared to healthy subjects ( $t_{(17)} = 4.401, p = 0.001$ ). One healthy control (male, age = 81 years old) was excluded from the analysis since the subject's movement data in terms of movement onset time and velocity was deviated markedly from other healthy controls.

Table 4.1 Demographic Characteristic.

	Age, y	Gender	Time Poststroke, y	Paresis	Lesion location	Dominant Side	FM-UE (/66)	FM-LE (/34)	CB&M (/96)*
Stroke #1	75.73	M	14.00	R	Cortical & subcortical	R	49	31	58
Stroke #2	63.36	M	5.91	R	Cortical & subcortical	R	39	25	48
Stroke #3	77.63	M	20.51	L	Cortical	L	33	19	30
Stroke #4	62.58	F	7.55	L	Cortical & subcortical	R	30	17	27
Stroke #5	68.14	M	8.81	L	Cortical & subcortical	R	62	26	30
Stroke #6	70.33	F	16.40	R	Subcortical	R	26	21	16
Stroke #7	74.23	F	51.26	L	Subcortical	L	36	19	17
Stroke #8	64.10	M	0.97	R	Subcortical	R	65	34	78
Stroke #9	55.99	M	2.26	R	Subcortical	R	65	34	75
Stroke #10	79.29	M	1.29	L	Subcortical	R	55	29	31
Stroke Mean $\pm$ SD	69.13 $\pm$ 7.61	7M/3F	12.9 $\pm$ 15.00	5R/5L	1 Cortical/5 Subcortical/ 4 Cortical & subcortical	8R / 2L	46.00 $\pm$ 15.06	25.50 $\pm$ 6.36	41.00 $\pm$ 22.61
Controls Mean $\pm$ SD	66.08 $\pm$ 6.76	6M/3F	NA	NA	NA	8R / 1L	NA	NA	76.89 $\pm$ 11.76

### 4.7.1 The stroke group

#### 4.7.1.1 Incidence of SR response following LAS (Fig. 4.7)

Analysis in the incidence of SR showed differential effects of PMAs vs. M1 stimulation depending on the LAS timing in individuals with stroke. A significant interaction between Stimulation site  $\times$  LAS condition was found ( $F_{(1, 36)} = 7.246, p = 0.011$ ). Stratified analyses showed that SR incidence increased more after M1 stimulation compared to PMAs stimulation when the LAS was at  $-500$  ms ( $p = 0.023$ ) (Fig. 4.7A). In addition, after M1 stimulation, SR incidence increased when the LAS was at  $-500$  ms but decreased when the LAS was at  $-200$  ms (Fig. 4.7). In contrast, cathodal PMAs

caused a decrease in the SR incidence at both LAS time points – 500 ms and – 200 ms. This suggests a differential effect of PMAs vs. M1 stimulation on SR incidence depending on the LAS timing in individuals with stroke

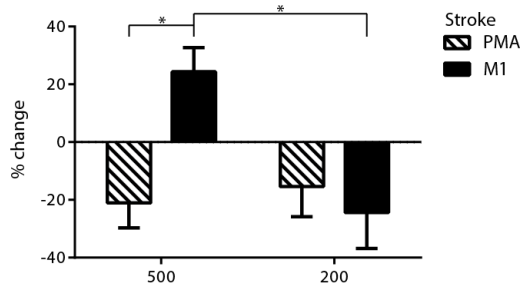


Figure 4.7 Mean change ( $\pm$ SE) of the incidence of SR response in stroke subjects when the LAS was presented at 500 and 200 ms before the go cue.

#### 4.7.1.2 APA-reach performance

Reaching responses: In individuals with stroke, there was a significant Stimulation site  $\times$  LAS condition interaction ( $F_{(3, 72)} = 4.708, p = 0.005$ ) in AD EMG onset (Fig. 4.8). Stratified analyses showed that there was effect of LAS condition after anodal M1 stimulation showing that a decrease in AD EMG onset when the LAS was at – 500 ms compared to when the LAS was at 0 ms ( $p = 0.026$ ). Stratified analyses also showed that there were effects of Stimulation site when the LAS was at – 500 ms ( $p = 0.05$ ), 0 ms ( $p = 0.053$ ), and control reach condition ( $p = 0.058$ ) although the difference was outside the significance cutoff. When the LAS was at – 500 ms, the increase of AD onset was larger after cathodal PMAs stimulation than M1 stimulation in individuals with stroke. However, when the LAS was at 0 ms or in the control reach condition, the increase of AD was larger after anodal M1 stimulation than PMAs stimulation. For the other reach-related variables including reach onset, reach peak velocity, and AD integrated EMG, there were no significant Stimulation site  $\times$  LAS condition interactions, or the main effects of Stimulation site and LAS condition.

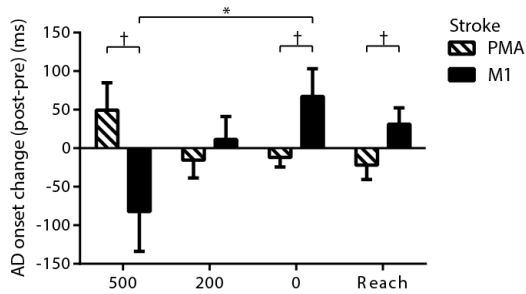


Figure 4.8 Mean change ( $\pm$ SE) in AD EMG onset in stroke subjects across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$  and †  $p < 0.1$ .

APA responses: In individuals with stroke, there was a significant Stimulation site  $\times$  LAS condition interaction ( $F_{(3, 61.587)} = 3.146, p = 0.017$ ) on nonparetic TA onset. Stratified analyses showed that there was a significant effect of Stimulation site when the LAS was at -500 ms ( $p = 0.018$ ). Specifically, the nonparetic TA onset was later after cathodal PMAs stimulation than after anodal M1 stimulation at LAS time point -500 ms (Fig.4.9). In addition, after cathodal PMAs stimulation, there was a larger increase of nonparetic TA onset time when the LAS was at -500 ms compared to the control reach condition where there was no LAS applied ( $p = 0.045$ ). The other APA-related variables including APA onset, APA magnitude, and TA integrated EMG were not affected by Stimulation site, LAS condition, and Stimulation site  $\times$  LAS condition interaction.

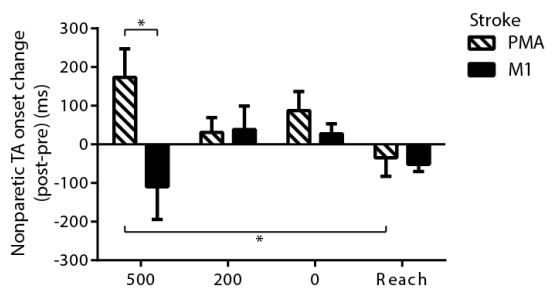


Figure 4.9 Mean change ( $\pm$ SE) in nonparetic TA EMG onset in stroke subjects across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

APA-reach sequence: There was no main effects of Stimulation site, LAS condition, and Stimulation site  $\times$  LAS condition interaction on the lag between APA and reach onsets in individuals with stroke.

Trunk contribution during movement execution: A significant main effect of stimulation site was found on the trunk flexion ( $F_{(1, 66)} = 8.622, p = 0.005$ ). In Fig. 4.10A, the trunk flexion had a larger increase after anodal M1 stimulation compared to after cathodal PMAs stimulation in individuals with stroke. Marginal main effects of Stimulation site on trunk rotation and paretic ES integrated EMG were found (trunk rotation:  $F_{(1, 66)} = 3.294, p = 0.074$ ; ES integrated EMG:  $F_{(1, 59.806)} = 3.342, p = 0.073$ ). In Fig 4.10B, after anodal M1 stimulation, there was a trend of greater increase in the trunk rotation compared to after cathodal PMAs stimulation. In Fig 4.10C, after anodal M1 stimulation, stroke subjects demonstrated a trend of greater reduction in paretic ES integrated EMG compared to after cathodal PMAs stimulation. For the trunk-pelvic rotation difference, a main effect of Stimulation site was found in individuals with stroke ( $F_{(1, 75)} = 4.721, p = 0.033$ ). Anodal M1 stimulation contributed to a greater decrease in the trunk-pelvic rotation difference than cathodal PMAs stimulation (Fig. 4.10D). No significant main effects of LAS condition and Stimulation site  $\times$  LAS condition interaction were found for the above outcome variables.

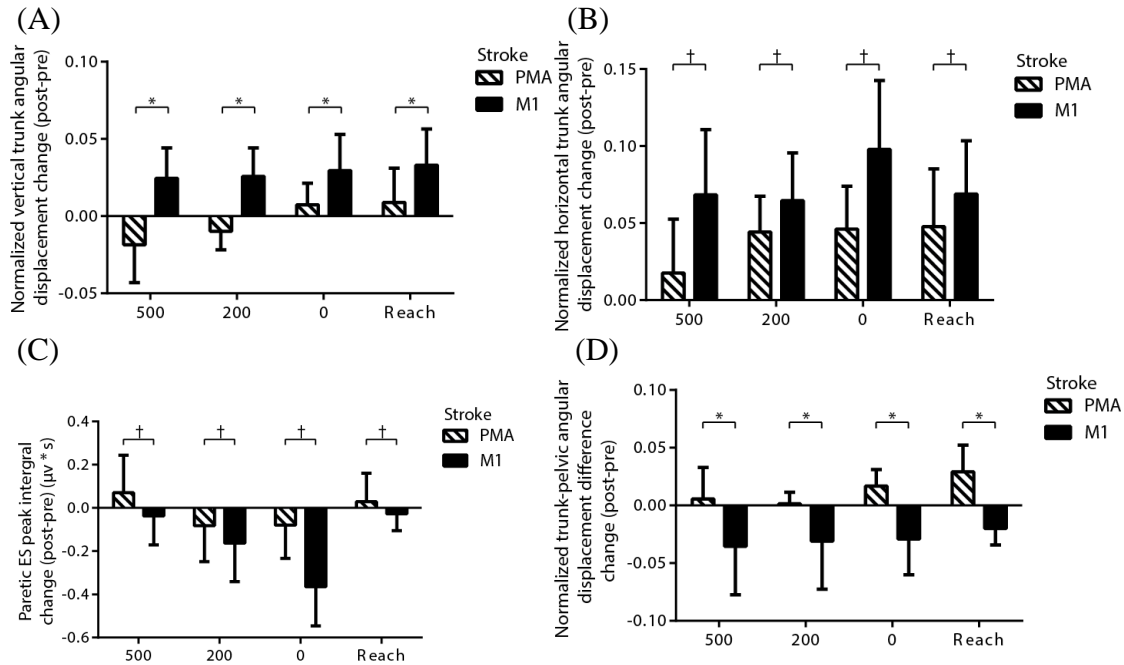


Figure 4.10 Mean change ( $\pm$ SE) in (A) trunk flexion, (B) trunk rotation, (C) paretic ES integrated EMG, and (D) trunk-pelvic rotation difference in stroke subjects across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$  and †  $p < 0.1$ .

#### 4.7.1.3 Neurophysiological measurement

In individuals with stroke, MEPs were absent in some of subjects. The number of subjects who we were able to retrieve MEPs for BB was 6 and for TA was 8 subjects for the M1 stimulation. For the PMAs stimulation, we were able to retrieve MEPs in 5 subjects for BB and in 7 subjects for TA. No significant difference in MEP amplitudes before and after tDCS was found in individuals with stroke.

## 4.7.2 The healthy group

### 4.7.2.1 *Incidence of SR response following LAS (Fig. 4.11)*

In healthy subjects, there were no main effects of Stimulation site ( $F_{(1, 25)} = 0.048, p = 0.828$ ), LAS condition on SR incidence ( $F_{(1, 25)} = 2.625, p = 0.118$ ), and Stimulation site  $\times$  LAS condition interaction (Fig. 4.11).

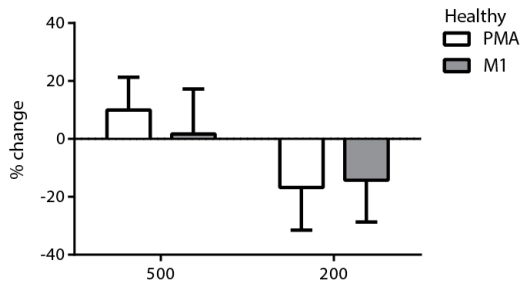


Figure 4.11 Mean change ( $\pm$ SE) of the incidence of SR response in healthy subjects when the LAS was presented at 500 and 200 ms before the go cue.

### 4.7.2.2 *APA-reach performance*

Reaching responses: Effects of PMAs vs. M1 stimulation were found on the change in reach peak velocity and AD integrated EMG in healthy subjects. Main effects of comparing Stimulation site on reach peak velocity and integrated AD EMG were found (peak velocity:  $F_{(1, 59)} = 4.933, p = 0.030$ ; AD integrated EMG:  $F_{(1, 59)} = 7.883, p = 0.007$ ) (Fig 4.12A and 4.12B). After anodal M1 stimulation, the reach peak velocity and integrated AD EMG decreased compared to after anodal PMAs stimulation. No significant main effect and Stimulation site  $\times$  LAS condition interaction were found on reach peak velocity and integrated AD EMG. For the reach onset and AD EMG onset, there were no significant Stimulation site  $\times$  LAS condition interactions, or the main effects of Stimulation site and LAS condition.

APA responses and APA-reach sequence: No effects of Stimulation site, LAS condition, and Stimulation site  $\times$  LAS condition interaction were found on the lag between APA and reach onsets, APA onset, APA magnitude, TA EMG onset, and TA integrated EMG.

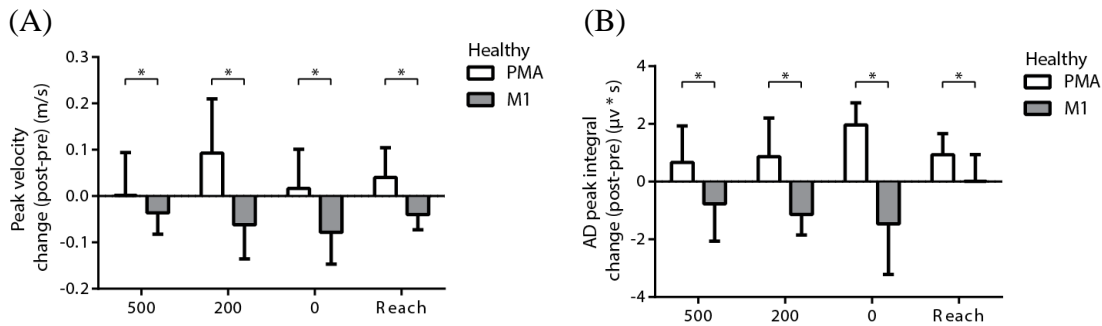


Figure 4.12 Mean change ( $\pm$ SE) in (A) peak velocity and (B) AD integrated EMG in healthy subjects across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

Trunk contribution during movement execution: In healthy subjects, there was a marginal main effects of Stimulation site on the change in the trunk flexion ( $F_{(1, 59)} = 3.930, p = 0.052$ ), significant main effects of Stimulation site on the trunk-pelvic rotation difference ( $F_{(1, 59)} = 5.156, p = 0.027$ ), and on the ES integrated EMG ( $F_{(1, 54.801)} = 11.564, p = 0.001$ ). The trunk flexion (Fig. 4.13A) and ES peak integral (Fig. 4.13B) had a larger decrease after anodal PMAs stimulation compared to after anodal M1 stimulation. In Fig 4.11C, anodal PMAs stimulation resulted greater increase of the the trunk-pelvic rotation difference compared to M1 anodal stimulation (Fig. 4.13C). No significant main effects of LAS condition and Stimulation site  $\times$  LAS condition interaction were found for the above outcome variables.

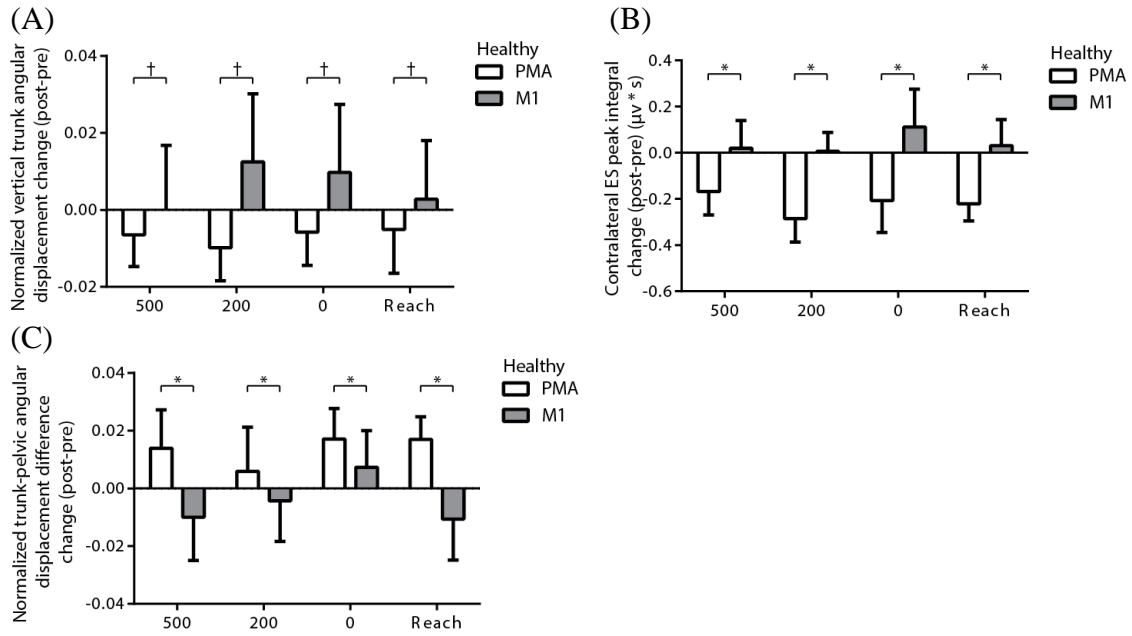


Figure 4.13 Mean change ( $\pm$ SE) in (A) trunk flexion, (B) integrated ES EMG, and (C) trunk-pelvic rotation difference in healthy subjects across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$  and †  $p < 0.1$ .

#### 4.7.2.3 Neurophysiological measurement:

No significant difference in MEP amplitudes was found before and after tDCS in the healthy subjects.

## 4.8 Discussion

The present study was conducted to determine the role of PMAs in posture, movement planning, preparation and execution during a standing reaching task in individuals with stroke and healthy subjects. Our main findings were that anodal tDCS over M1 was more effective in increasing the SR incidence than cathodal tDCS over PMAs in individuals with stroke. It has been suggested that pontomedullary reticular formation (PMRF) is critically involved in generating posture responses (Schepens & Drew, 2003; Yakovenko & Drew, 2009) and in the SR responses (Nonnekes, Oude Nijhuis et al., 2014). In our conceptual model (Fig 4.1), we proposed that the abnormal hyperexcitability in PMAs due to chronic stroke may lead to excessive inhibitory input via the cortico-reticulospinal pathway, and consequently impairs posture and movement planning, preparation, and execution. We hypothesized that down-regulating the hyperexcitability in PMAs by applying cathodal tDCS over these regions may restore the inhibitory input from PMAs to the PMRF (Fig 4.14A). Opposite to our hypothesis, our findings showed an increase in SR incidence and a decrease in muscle activation onset latency when the LAS was applied at – 500 ms after anodal M1 stimulation compared to cathodal PMAs stimulation in individuals with stroke (Fig 4.14B). This is consistent in part with Nonnekes et al. (2014) who showed a decrease in reaction time irrespective of whether or not an LAS was given at the imperative stimulus after anodal M1 stimulation (Nonnekes et al., 2014). The author concluded that the subcortical structures can possibly be facilitated by an enhancement of the cortico-reticular drive or by direct excitations caused by the applied current. One animal study also showed that tDCS over the motor cortex of anesthetized cats facilitated subcortical structures either directly or indirectly

(Bolzoni, Pettersson, & Jankowska, 2013). Moreover, Wagner and colleagues showed possible direct subcortical facilitation from the spread of current during tDCS application and importantly the current density distributions were different in the stroke model compared to the healthy head model (Wagner et al., 2007). In the present study, it is possible that application of anodal tDCS over M1 but not cathodal tDCS over PMAs in individuals with stroke facilitate directly or indirectly the subcortical structures such as PMRF. With our stimulation paradigm (i.e., tDCS of 1mA for 20 mins), rather than remediating the excessive inhibitory input from the PMAs onto the subcortical brainstem by applying cathodal tDCS over PMAs, the direct or indirect subcortical facilitation from anodal tDCS over the region of M1 may be more effective modulating brainstem neuronal excitability and in turn improving movement planning and preparation. Another plausible explanation is that given that PMAs include a larger cortical area compared to M1, a higher intensity or longer duration of tDCS is required to induce changes in PMAs. Taken together, although the findings from this study are not consistent with our hypothesis, our conceptual model does not mutually exclude the possible subcortical facilitation mechanisms.

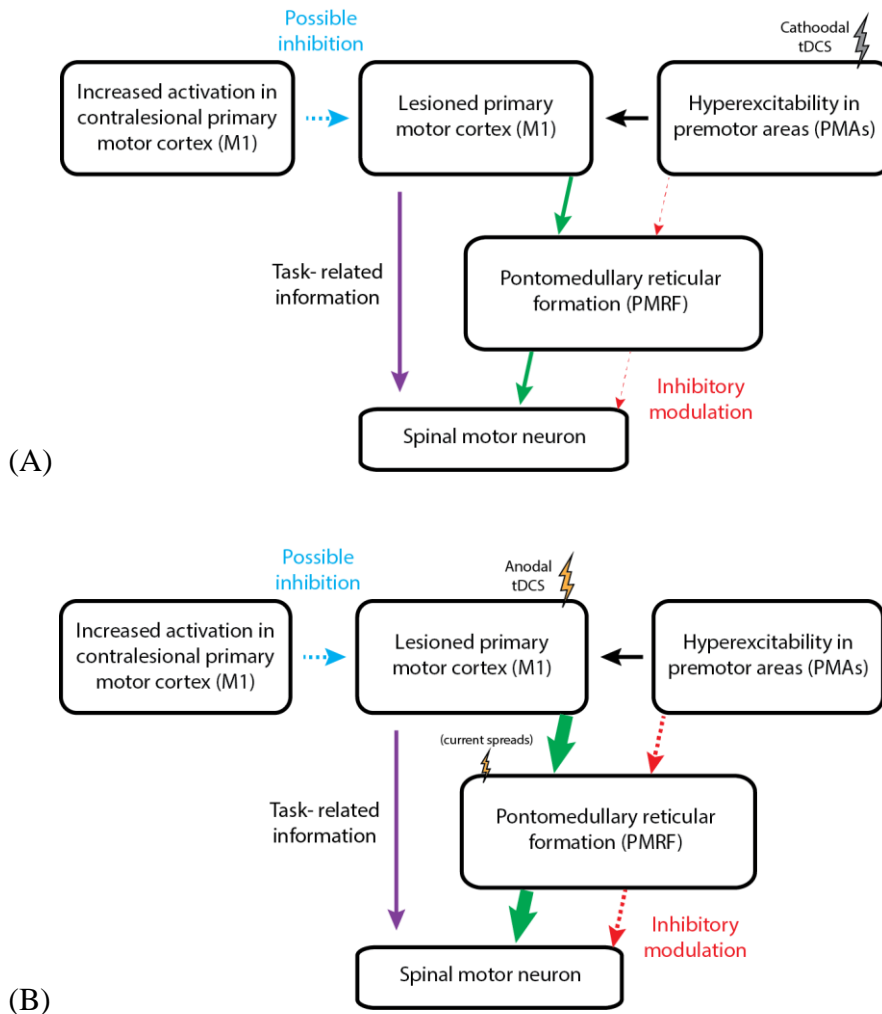


Figure 4.14 Schematic representation of proposed neuromodulation of (A) cathodal tDCS over PMAs and (B) anodal tDCS over M1 related to posture and movement planning and preparation in individuals with stroke. In figure (A), we hypothesized that cathodal tDCS over PMAs would down-regulate the hyperexcitability in this region and consequently restore the excessive inhibitory input (red dashed arrow) from PMAs to the PMRF via cortico-reticulospinal tract. In figure (B), based on our findings, it is possible that application of anodal tDCS over M1 facilitates the subcortical PMRF via the cortico-reticular drive (green arrow) or direct excitations caused by the applied current.

Another factor that influenced the effect of tDCS on the incidence of SR response was the LAS timing. A greater increase in the incidence of SR responses following anodal M1 stimulation was only found at the LAS time point – 500 ms but not at – 200 ms. One possible explanation is that during the time course of movement planning and preparation, the excitability at the cortical and subcortical levels changes gradually. Cohen et al. (2010) proposed that during preparation for movement there were two pathways controlling spinal motorneuronal circuitry in order to preplan the movement and avoid premature release of the movement. The excitatory input which originates from PMAs and relays via M1 to spinal cord transmits task-related information while the global inhibition originates from PMAs and relays via subcortical level to spinal circuitry (i.e., cortico-reticulospinal pathway) prevents premature motor action. It has been suggested that the corticospinal excitability during movement planning and preparation undergoes progressive changes due to global inhibition (van Elswijk, Schot, Stegeman, & Overeem, 2008). It is possible that the dynamic changes of inhibitory inputs onto spinal motorneuronal circuitry during movement planning and preparation lead to differential effects of tDCS on the incidence of SR responses depending on the LAS timing.

In the current study, there were no detectable neurophysiological change of MEP amplitudes following PMAs and M1 stimulation but posture and movement planning, preparation, and execution were modified after tDCS. One possible reason for non-significant changes in MEP amplitudes is inter-individuals response variability. Previous studies have reported that the effects of tDCS on MEP amplitudes elicited by single-pulse TMS as a measure for corticospinal excitability are highly variable (Lopez-Alonso, Fernandez-Del-Olmo, Costantini, Gonzalez-Henriquez, & Cheeran, 2015; Wiethoff,

Hamada, & Rothwell, 2014). One study showed that approximately 50% of healthy individuals had poor or no response to tDCS as measured by MEP amplitudes and only 36% of individuals had expected responses after tDCS (i.e., facilitatory effect after anodal M1 stimulation and inhibitory effect after cathodal M1 stimulation) (Wiethoff et al., 2014). Lopez-Alonso (2015) also used MEP as an indicator and showed that approximately 40% of healthy subjects were non-responders after anodal tDCS over M1. Another possible reason is that the changes in cortical excitability after tDCS are the result of intracortical facilitation or inhibition not corticospinal excitability as shown in MEP amplitudes elicited by single-pulse TMS. One study by Nitsche et al. (2005) used paired-pulse TMS with different interstimulus interval and found that following tDCS intracortical inhibition and facilitation were modified (Nitsche et al., 2005). In the present study, intracortical inhibition and facilitation were not measured, therefore, the resulting changes in cortical excitability due to tDCS may not have been captured. Altogether, the fact that the differential effect of PMAs vs. M1 stimulation on posture and movement planning, preparation, and execution confirms that focal stimulation of tDCS induces changes according to the stimulation site. This may suggest that single-pulsed MEP amplitude may not be a preferred indicator of neurophysiological changes obtained by tDCS.

Our findings show a differential effect of PMAs vs M1 stimulation on trunk contribution during reaching execution and reaching performance across LAS conditions. Generally, we found that there was a greater increase in trunk movement after anodal M1 stimulation compared to anodal PMAs stimulation in healthy subjects and anodal M1 compared to cathodal PMAs stimulation in individuals with stroke. One possible

explanation is that the anodal electrode placement over M1 stimulation included the trunk representation since it was at the midpoint of hotspots of BB and TA. Based on the homunculus map of a human brain, the area representing the trunk is in the middle of arm and leg areas. Thus, the M1 stimulation in the present study may also affect trunk performance. Another plausible explanation is the subcortical facilitation described in the previous section. Since the PMRF is known to be involved in generating compensatory postural responses (Schepens & Drew, 2003; Yakovenko & Drew, 2009), the direct or indirect facilitation induced by anodal M1 stimulation may increase the excitability in the PMRF and subsequently alter trunk involvement during reaching.

In healthy subjects, differential effects of anodal PMAs vs. M1 stimulation were found on peak velocity of reach. One study has demonstrated that anodal tDCS over premotor cortex improved the intracortical excitability of the ipsilateral M1 as shown by decreased intracortical inhibition and increased paired-pulse excitability measured by TMS (Boros, Poreisz, Munchau, Paulus, & Nitsche, 2008). However, another study found that anodal tDCS over M1 during finger tapping resulted in a decrease in the BOLD response in the supplementary motor area measured by fMRI (Antal, Polania, Schmidt-Samoa, Dechent, & Paulus, 2011). Although the physiological mechanisms underlying BOLD signal and measurements of MEPs are different, the above studies may still reflect the different interconnectivity from PMAs to M1 vs. from M1 to PMAs. Several studies also showed improved motor performance after anodal tDCS over PMAs (Pavlova, Kuo, Nitsche, & Borg, 2014; Vollmann et al., 2013; Wade & Hammond, 2015). Thus, it is possible that use of tDCS to modulate PMAs activity as used in the present study may

yield additional specific beneficial effects on movement performance such as reach peak velocity compared to modulating M1 activity.

There are several limitations inherent in the study design. One major challenge of our study was that we aimed to modulate PMAs and M1 separately. Even though small tDCS electrodes were used over both target areas in an attempt to increase the focality of stimulation, the possibility that during PMAs stimulation, M1 region was also partly stimulated can not be ruled out, and vice versa. Nevertheless, differential effects of PMAs vs. M1 stimulation on variables of posture, movement planning, preparation and execution were demonstrated in the present study and provide credible evidence that modulation of these two areas by tDCS is plausible. Another limitation is that the absence of detectable MEP amplitudes changes following tDCS. The difficulty to record MEPs data in 20-30% of our stroke subjects, inter-individuals response variability, and inability to capture changes in cortical excitability by single-pulsed TMS protocol probably contributed to nonsignificant changes in MEP amplitudes. Future studies should also consider measuring cortical excitability changes following tDCS with a more comprehensive assessment by TMS in order to detect the modulation effect of tDCS.

#### **4.9 Conclusion**

The present results show that following the application of tDCS over the region of the PMAs or M1, “stimulation site”-specific changes were observed in posture and movement planning, preparation and execution in both individuals with stroke and healthy subjects. In addition, we also provide novel evidence that stroke-related deficits in movement planning and preparation as shown by an abnormal absence of SR

responses during the paretic arm reaching can be improved by application of anodal tDCS over the region of lesioned M1 and the enhancement effects are depending on the timing of the LAS. It is possible that either direct or indirect subcortical facilitation resulting from the anodal tDCS over M1 may offer a new neuromodulatory target to remediate the imbalance in neuronal excitability between PMAs and subcortical brainstem level, which in turn improve the posture and movement planning, preparation, and execution in individuals with stroke.

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## 5 CHAPTER V: SUMMARY AND FUTURE RESEARCH DIRECTIONS

### 5.1 Summary

The overall objective of this dissertation was to investigate posture, movement planning, preparation, and execution during a standing reaching task in individuals with chronic stroke and healthy age-matched subjects. To examine movement planning and preparation, the presence of StartReact (SR) responses in anticipatory postural adjustments (APAs) and reach movement triggered by a loud acoustic stimulus (LAS) was assessed. The LAS was presented at different time points during an instructed delayed paradigm relative to the imperative “go” cue in a simple reaction time task. In Chapter 2, we demonstrated how posture, movement preparation, and execution were impaired during the paretic arm reaching in individuals with stroke and healthy controls. In Chapter 3, we extended the findings from Chapter 2 to show that these impairments were also present during the nonparetic arm reaching, which indicated a system-wide issue in the central nervous system (CNS), however, with more significant deficits during the paretic arm reaching. In Chapter 4, we demonstrated the differential effects of tDCS over PMA and M1 on posture, movement planning, preparation, and execution.

#### 5.1.1 Chapter 2

Chapter 2 is a published study. In Chapter 2, we investigated movement preparation of both APAs and goal-directed movement during a standing reaching task with the paretic arm in individuals with stroke and healthy controls. The results showed that individuals with stroke demonstrated a marked reduction in the occurrence of the SR responses for both APA and reach indicating movement preparation dysfunction for the paretic arm reaching movement. When the LAS was presented at the “go”, there was

earlier but not significant differences in APA onset latency compared to reaching without LAS and significant delays in reach onset latency in stroke subjects when compared to healthy control subjects with or without LAS. These findings differ from previous studies showing intact SR responses in individuals with stroke in single joint UE movements and a gravity eliminated reaching task while seated (Honeycutt & Perreault, 2012; Honeycutt et al., 2015; Marinovic et al., 2016). One possible explanation is the difference in complexity between the tasks. The present experimental task involved a multi-joint antigravity reaching movement while standing, which required the coordination and integration between two systems: postural control and goal-directed reaching. The complexity of integrating postural and goal-directed reach systems may require more elaborate preparation and planning. We also found that early activation of electromyography (EMG) in biceps brachii with a delay of the reach onset compared to reaching without LAS. This task-inappropriate flexor activity likely resulting from unsuppressed or hypermetric classical startle reflex was shown to increase with impairment in individuals with stroke. Altogether, our findings suggested that movement preparation following stroke for a complex multi-segmental movement may not be as well-preserved and the heightened classical startle reflex may interfere with the movement.

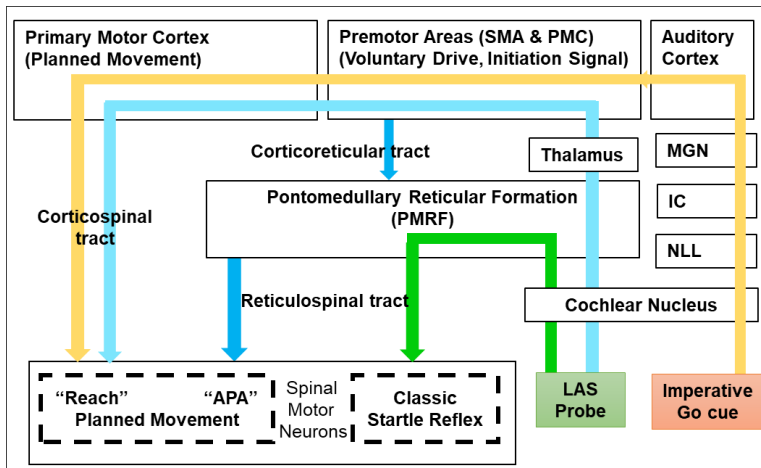
### 5.1.2 Chapter 3

In Chapter 3, we addressed: 1) posture and movement planning, preparation, and execution as measured by the incidence, onset, and magnitude of SR responses, and 2) the APA-reach sequence as measured by spatial and temporal variables of APA-reach sequence, and 3) the role played by the trunk in APA-reach sequence as measured by the

trunk rotation during voluntary reaching in standing in individuals with chronic hemiparesis and healthy controls. The key finding suggested that impaired movement planning and preparation measured by the incidence of SR responses was a system-wide problem in the CNS involving both lesioned and contralesional side in persons after stroke. We also found that although individuals with stroke preserved better control of APA and reach during the nonparetic arm compared to the paretic arm reaching movement, the APA and reach onsets were later and reach velocity was slower in comparison with the healthy controls. Lastly, individuals with stroke tended to use the “trunk and pelvic” compensatory strategy as shown by an earlier trunk and pelvic rotation onset and greater trunk and pelvic rotation to transport the paretic arm toward the target.

We proposed an adapted model for the normal release of the planned movement sequence which is illustrated in Fig. 5.1. Based on our findings showing abnormal movement planning and preparation following stroke, we proposed another model for individuals with stroke which is illustrated in Fig. 5.2 A and B. In this model, we proposed that PMAs normally have a modulatory role in StartReact responses through inhibitory input to brainstem motor circuits and/or spinal cord via the pontomedullary reticular formation (PMRF). Hence, during the nonparetic arm reaching, abnormal hyperexcitability in PMAs due to chronic stroke (Ward et al., 2003) leads to excessive inhibition of the pontomedullary reticular formation (PMRF) and/or spinal cord resulting in an absence of and/or reduced magnitude of SR responses and a disruption of the normal sequencing between posture and movement (Fig 5.2A). However, during the paretic arm reaching, the neuronal networks responsible for the paretic arm movements involves additional abnormal inhibition such as increased inhibition from contralesional

to ipsilesional M1 (Fig 5.2B). Thus, the neuronal excitability between the cortical and subcortical levels is impaired and subsequently affects the posture, movement planning, preparation, and execution for the paretic arm reaching to a greater extent in comparison with the nonparetic arm reaching.



Adapted from Alibiglou & Mackinnon (2012)

Figure 5.1 The proposed model for the triggering process of a StartReact (SR) response, voluntary movement, and classic startle reflex. The yellow arrow shows the regular pathway for releasing a voluntary movement by a non-startling stimulus. The premotor areas including supplementary motor area (SMA) and premotor cortex (PMC) have input from the go cue via an auditory pathway and auditor cortex. Then the voluntary drive transmits to the primary motor cortex and triggers the release of the planned movement sequence. The blue arrows are the pathways, which an SR response can be released by a loud acoustic stimulus (LAS) via two possible tracts. The premotor areas have input from the LAS and have a voluntary drive that triggers the early release of the planned movement sequence at the level of cortex via the corticospinal pathway or corticoreticulo-spinal pathway. The green arrow represents the known pathway for the release of a classical startle reflex. An LAS travels to the pontomedullary reticular formation (PMRF) and results in a classical startle reflex. Abbreviations: APA: anticipatory postural adjustment. NLL: nuclei of the lateral lemniscus; IC: inferior colliculus; MGN: medial geniculate nucleus.

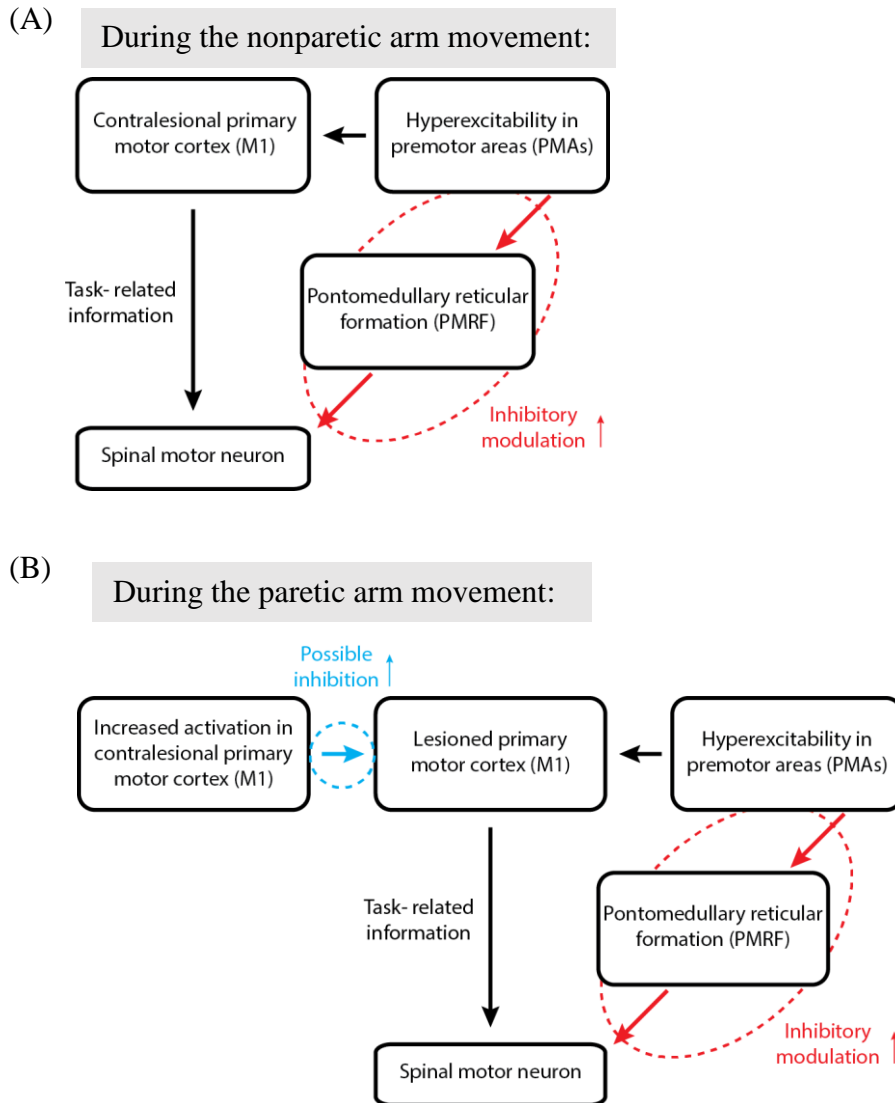


Figure 5.2 This model is adapted from Cohen (2010). The conceptual model for abnormal movement planning and preparation following stroke. During movement planning and preparation, normally two primary pathways affect spinal motoneuronal circuitry. The first pathway delivers task-related information from PMAs to M1 and subsequently to spinal cord over the corticospinal pathway. The second cortico-reticulospinal pathway from PMAs to spinal cord via PMRF applies inhibitory modulation in order to prevent premature release and specify magnitude scaling of the motor action. (A) After stroke, hyperexcitability in PMAs leads to excessive inhibitory input via the cortico-reticulospinal pathway, and consequently impairs movement planning, preparation and performance as shown by absent/reduced StartReact (SR) response during the nonparetic arm reaching. (B) During the paretic arm reaching, there is possible inhibition from increased activation in contralesional primary motor cortex (M1) on the ipsilesional M1. Thus, movement planning, preparation, and performance is impaired to a greater extent compared to during the nonparetic arm reaching movement.

### 5.1.3 Chapter 4

In Chapter 4, we aimed to address the modulatory role of the Premotor areas (PMAs) (supplementary motor area and premotor cortex) in SR responses following 20 mins of 1) applying anodal transcranial direct current stimulation (tDCS) over PMAs in healthy subjects and 2) applying cathodal tDCS over PMAs in persons with stroke. M1 was another stimulation site for anodal tDCS for both groups. According to our original conceptual model for abnormal movement planning and preparation in individuals with stroke, remediating the excessive inhibition from PMAs to the PMRF by the application of cathodal tDCS may result in enhancing posture and movement planning and preparation following stroke (Fig. 5.3A). Our hypotheses were as follows: 1) By mimicking the pathophysiologic effects of stroke, anodal tDCS over PMAs, would induce hyperexcitability in healthy subjects, resulting in diminished StartReact responses as measured by reduced incidence, magnitude, and slower onset of the SR responses. 2) Applying cathodal tDCS over PMAs would reduce the neuronal excitability in PMAs thereby helping to improve posture and movement planning and preparation in persons with stroke, as measured by increased incidence, magnitude, and faster onset of the responses. However, opposite to our hypothesis, our main finding was that anodal tDCS over M1 was more effective in increasing the SR incidence than cathodal tDCS over PMA in individuals with stroke. As shown in figure 5.3B, the possible explanation is the application of anodal tDCS over M1 may yield direct or indirect facilitation on the subcortical structures such as PMRF, which may, in turn, improving posture and movement planning and preparation in individuals with stroke. While the results were not

consistent with our hypothesis, the possible subcortical facilitation mechanism does not refute our conceptual model.

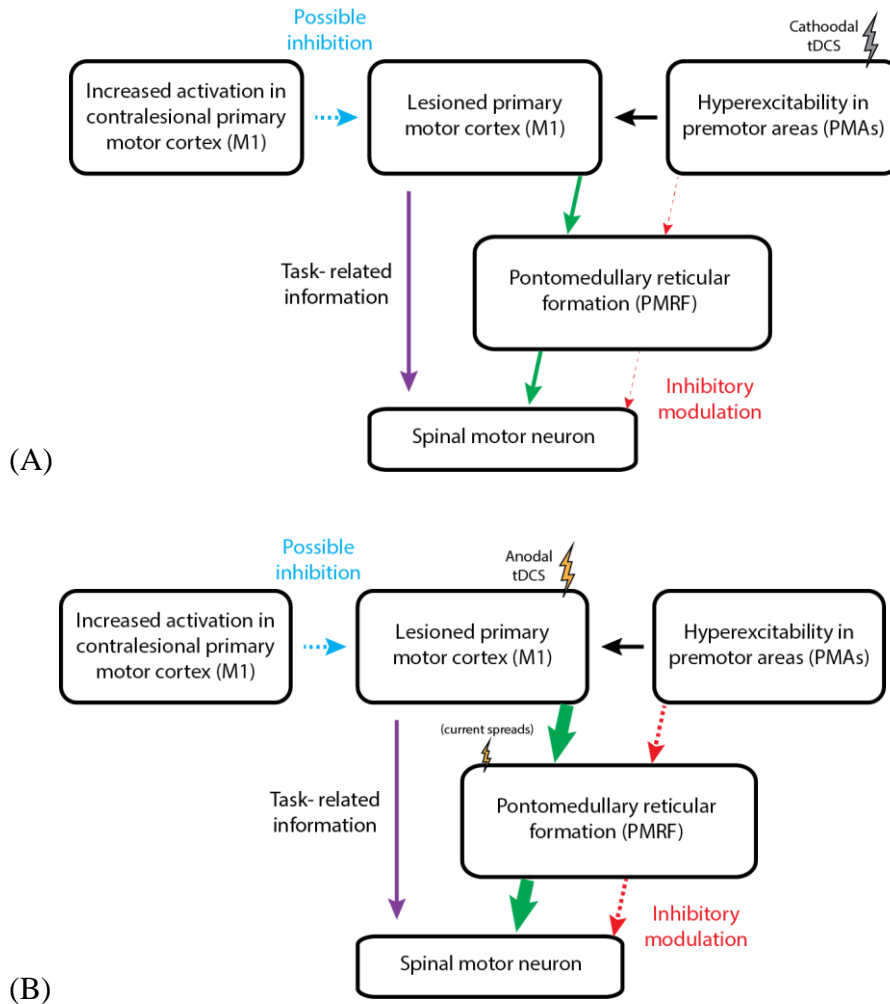


Figure 5.3 Schematic representation of proposed neuromodulation of (A) cathodal tDCS over PMAs and (B) anodal tDCS over M1 related to posture and movement planning and preparation in individuals with stroke. In figure A, we hypothesized that cathodal tDCS over PMAs would down-regulate the hyperexcitability in this region and consequently restore the excessive inhibitory input (red dashed arrow) from PMAs to the PMRF via cortico-reticulospinal tract. In figure B, based on our findings, it is possible that application of anodal tDCS over M1 facilitates the subcortical PMRF via the cortico-reticular drive (top green arrow) or direct excitations caused by the applied current.

## 5.2 Future research directions

### 5.2.1 Chapter 2

#### 1. Effect of task complexity on movement preparation

A marked reduction in the incidence of SR responses during standing and reaching with the paretic arm reaching in individuals with chronic stroke was found. This suggests a system-wide posture and movement preparation impairments following stroke. Our findings were opposite to previous studies which showed comparable SR responses in individuals with stroke and healthy controls (Honeycutt & Perreault, 2012; Honeycutt, Tresch, & Perreault, 2015; Marinovic et al., 2016). One possible reason is that the complexity of the movement involved in a reaching task may affect SR responses triggered by an LAS. Previous studies examined SR responses in a single joint upper extremity (UE) movement or supported reach movement eliminating gravity involvement whereas our task required a multi-joint antigravity reaching movement while standing requiring the coordination and integration between two systems: postural control and goal-directed reaching. Future studies should examine how task complexity affects SR responses in individuals with stroke and in healthy controls. One can examine the effects of gravity on SR responses in movements with and without gravity involvement (e.g., free reach vs. supported reach). One can also examine how posture affects SR responses by comparing SR responses in sitting vs. standing. In addition, the degree of cortical involvement in a functional task may also play an important role in SR responses. For example, the SR responses in a stepping task or automatic postural responses to external perturbations (more subcortical mediated) vs. reach task while standing (with more

cortical involvement) may also help to tease out the deficits in movement preparation in individuals with stroke.

### 5.2.2 Chapter 3

We found generally impaired movement planning and preparation during a complex goal-directed reaching movement while standing, which involved both lesioned and contralesional sides in individuals with stroke. Since no previous studies have investigated this issue during the nonparetic side movement in other tasks, it is necessary to understand to what extent that the ability to plan a movement is preserved during the nonparetic side movement. Therefore, the future research direction that we proposed for chapter 2 regarding the effect of task complexity on posture and movement and planning preparation may also apply to chapter 3. In addition, we proposed the following future research direction based on the extended findings in Chapter 3.

#### 1. Effect of classical startle reflex on task performance

As discussed in chapter 2, the LAS that has been used as a probe to examine posture and movement planning and preparation may trigger classical startle reflex in individuals with stroke, which in turn interfere with the planned movement elicited by an LAS (Honeycutt & Perreault, 2012, 2014; McCombe Waller et al., 2016). As reported in our previous paper, presentation of the LAS at “go” lead to an earlier muscle activation in anterior deltoid, middle deltoid, and biceps brachii but delayed the forward reach onset (McCombe Waller et al., 2016). In some subjects with chronic stroke , we also observed early bilateral muscle activity in arm and leg muscles triggered by the LAS but not related to task performance as evident in our data from Chapter 3. This early bilateral muscle activity may be possibly due to heightened classical startle reflex that

subsequently interfere with or disrupt the planned APA-reach sequence not only during the paretic but also the nonparetic arm reaching movement. Celinskis et al. (2018) also found that bilateral early activity in thigh muscles during unexpected postural external perturbations interfered with balance recovery in individuals with stroke (Celinskis, Grabiner, & Honeycutt, 2018). Since the classical startle reflex can be modulated by the prepulse inhibition, a phenomenon that a decrease in the amplitude of a classical startle reflex when a weak stimulus is applied prior to the LAS (Brown et al., 1991; Valls-Sole et al., 1997). Future studies may use these features to potentially modulate the classical startle reflex and examine whether SR responses are present without the possible interference of the classical startle reflex.

## 2. Relationship between absent/ present SR responses to motor impairments, functions and task performance

Although there was generally absent SR response in individuals with stroke, three stroke subjects had a slightly higher incidence of full or partial SR responses compared to the other individuals with stroke. Moreover, we found a trend of higher incidence of partial SR response during the nonparetic arm reaching compared to the paretic arm reaching. The reason why some stroke subjects were different from the others in terms of the incidence of SR responses is still unknown. It is important to discover the relevance of preserving full or partial SR responses with level of impairments or functions. Future studies should examine how presence or absence in SR responses is related to impairments, functions, or performance with a larger sample size and a wider range of impairment level in individuals with stroke. To answer these questions will require a larger sample size, we can evaluate if the person with stroke has a high incidence of SR

responses has higher motor functions. Also, we can examine if the presence of SR responses is related to better movement performance in a given trial. In addition, monitoring cortical activity by using electroencephalography (EEG) or functional near-infrared spectroscopy (fNIRS) during the movement preparation period of a task, performed by individuals with stroke may also help us tease out why some subjects are responders of SR responses and others are not.

### 3. Whole-body reaching training following stroke

In this chapter, we found a significant absence of SR response and impaired APA-reach performance as measured by later APA and reach onsets, and slower reach peak velocity during the nonparetic arm reaching in individuals with stroke compared to the healthy controls, indicating impaired posture and movement planning, preparation, and execution. One study by Saito (2014) demonstrated that reach performance and APAs improved after repeated whole-body reaching training emphasizing on speed in healthy young subjects and the APA learning effects were maintained and were generalized to the untrained arm. In addition, the changes in APA occurred earlier than the improvements in reaching performance and may contribute to the better reaching performance. Therapists should develop an intervention that includes not only the paretic but also the nonparetic arm training with a simultaneously postural control element (e.g., repetitive training of the whole-body reaching movement emphasizing on speed) to facilitate the integration of the goal-directed reaching and postural control systems. Future studies should examine the effect of repetitive training of the fast whole-body reaching movement on movement planning, preparation, and execution of APA-reach sequence in individuals with stroke.

### 5.2.3 Chapter 4

#### 1. Verification of hyperexcitability in PMAs in individuals with stroke

One major limitation of this study was that we were not able to verify if the stroke subjects had increased activity in PMAs before the testing. Our conceptual model was that hyperexcitability in PMAs due to chronic stroke applies abnormal suppression to the subcortical PMRF and subsequently impairs posture and movement planning, preparation, and execution as shown by a marked absence of SR responses and impaired APA-reach sequence. We hypothesized that by application of cathodal tDCS over PMAs to down-regulate the hyperexcitability in PMAs in individuals with stroke will restore the abnormal inhibition modulation from PMAs to the subcortical PMRF and consequently improve the outcomes. However, we found that compared to cathodal tDCS over PMAs, anodal tDCS over M1 was more effective in enhancing the movement planning and preparation as demonstrated by increased the incidence of SR responses. One possible explanation that PMAs stimulation did not work was that our stroke subjects might not have an abnormal increase in activation in PMAs before the testing. Therefore, cathodal tDCS over PMAs did not work as we anticipated to normalize the hyperexcitability in PMAs. Future studies may utilize neuroimaging tools to verify if hyperexcitability in PMAs is present during reaching movement. One neuroimaging tool that we may use is functional near-infrared spectroscopy (fNIRS). In comparison with common neuroimaging tools such as MRI that is expensive and has limitations on the movements that can be performed in the MRI, the portable, low-cost, and non-invasive fNIRS allows us to monitor and investigate real-time cortical brain activity during functional activities in the clinical environments and everyday settings. It provides information regarding

brain activation through monitoring of blood oxygenation and blood volume in the cortex (Mihara & Miyai, 2016). By using fNIRs, we can verify if the stroke subjects have abnormal hyperexcitability in PMAs during reaching movement in standing. To validate our conceptual model, we can then examine if the cathodal tDCS over PMAs can down-regulate the excitability following stimulation and consequently improve movement planning and preparation as measured by SR responses in those stroke subjects who have abnormal hyperexcitability in PMAs.

## 2. Address the possible explanations for findings in Chapter 4

In this chapter, our main finding was that anodal tDCS over M1 was more effective in increasing the SR incidence than cathodal tDCS over PMAs in individuals with stroke. This is opposite to our hypothesis that down-regulating the hyperexcitability in PMAs by applying cathodal tDCS over these regions would restore the inhibitory input from PMAs to the PMRF, which in turn, would be more effective in increasing the SR incidence than anodal tDCS over M1. One possible explanation is that with our stimulation paradigm (i.e., tDCS of 1 mA for 20 mins), application of anodal tDCS over M1 but not cathodal tDCS over PMAs in individuals with stroke facilitate directly or indirectly the subcortical PMRF. Future studies may compare the effect of anodal vs. cathodal tDCS over M1 in persons with stroke to see if the resulted changes are polarity-specific. If the anodal tDCS over M1 increases the incidence of SR responses, whereas the cathodal tDCS decreases it, M1 may be an alternative neuromodulatory target to facilitate subcortical structures either directly or indirectly.

Another possible explanation from the findings in Chapter 4 is that given PMAs include a larger cortical region compared to M1, our stimulation intensity or duration was

not sufficient to induce changes in excitability in PMAs. Our tDCS paradigm was set at an amplitude of 1mA and was delivered for 20 mins. Future studies may compare a higher intensity (e.g., 2 mA) or longer duration to our current stimulation paradigm of tDCS over PMAs and test if a more intense stimulation paradigm can induce changes in the outcomes.

### 3. Mechanisms underlying tDCS and selecting more effective stimulation paradigms

To our knowledge, this is the first study to show differential effects of tDCS over PMA vs. M1 on posture, movement, planning, preparation, and execution in individuals with stroke and healthy subjects. We found that anodal tDCS over M1 was more effective in enhancing movement planning and preparation as measured by increased SR incidences than cathodal tDCS over PMA in individuals with stroke. Similar to Nonnekes et al. (2004), we propose that the possible subcortical facilitation of the PMRF pathway had a positive effect to restore the imbalance between the cortical and subcortical excitability (Nonnekes et al., 2014). However, the mechanisms of how tDCS modulate brain excitability remain not well understood. Mechanisms underlying tDCS effects during stimulation has been suggested to solely depend on changes in membrane potential, which is supported by pharmacological approaches using ion channel blockage. Use of a sodium-channel blocker and calcium-channel blocker diminished the facilitatory effect of anodal tDCS in healthy subjects (Nitsche et al., 2003). The lasting effects of anodal tDCS have also been suggested to depend on membrane polarization as described above. Another possible mechanism appears to be the modification of intracortical neurotransmitter concentrations (Roche, Geiger, & Bussel, 2015). Stagg et al. assessed the effect of tDCS on modulation of cortical neurotransmitters (Stagg et al., 2009). It

seems NMDA-receptors and the GABA neurotransmitters may both contribute to the tDCS-induced after-effects. Although we did find positive effects of tDCS with our post-stimulation paradigm, it is essential to elucidate the mechanisms to help researchers determine the more effective stimulation paradigm and before it can be used routinely in rehabilitation clinics.

The tDCS parameters can be combined in multiple configurations, indicating many potential solutions to enhance the effect of tDCS. Variables that can be manipulated include manipulating current intensity (Jamil et al., 2017), current density (Nitsche et al., 2007), stimulation duration (Vignaud, Mondino, Poulet, Palm, & Brunelin, 2018), stimulation dosage (Nikolin, Martin, Loo, & Boonstra, 2018), stimulation site (Vollmann et al., 2013), electrode size (Nitsche et al., 2007), or electrode montage (Worsching et al., 2018). For example, in the present study, we used smaller stimulation electrodes to increase focality and higher current density as our purpose was to selectively stimulate PMA and M1. From all possible stimulation paradigms, it is necessary to determine or discover the most effective set of variables that enhance the recovery of desired treatment goals. Thus, with the elucidation of the mechanisms underlying tDCS effect and refinement of effective stimulation paradigm, given that tDCS is a noninvasive, low cost, and easy-to-apply tool, tDCS may be a therapeutic adjunct in rehabilitation for individuals with stroke.

#### 4. Inter- and intra- individual response to tDCS

Generally, previous studies have reported that even among healthy individuals, only approximately 50 % responded as expected to tDCS (Chew, Ho, & Loo, 2015; Lopez-Alonso et al., 2015; Wiethoff et al., 2014). The predictive response among stroke

subjects remain undetermined (Suzuki et al., 2012). One review has summarized likely factors that contribute to inter-individual response following tDCS such as baseline neural state and feature, anatomy, age, and lesion sites in the brain (Li, Uehara, & Hanakawa, 2015). For within- individuals variability, several studies have also demonstrated significant variability of response to tDCS across sessions (Chew et al., 2015; Dyke, Kim, Jackson, & Jackson, 2016; Horvath, Vogrin, Carter, Cook, & Forte, 2016; Wiethoff et al., 2014). In addition, the variability inherent in outcome assessments, specifically MEP amplitudes, may also contribute to the intra- and inter-individual variability in response to tDCS (Darling, Wolf, & Butler, 2006; Kiers, Cros, Chiappa, & Fang, 1993). The above reasons regarding inter- and intra-individual variability may contribute to why we did not show a significant change in corticospinal excitability as measured by single pulse MEPs following tDCS. Since it is not uncommon to observe inter- and intra-individuals variability of response to tDCS, it is critical to identify responders and non-responders to a given stimulation paradigm to maximize the beneficial effects of tDCS. Specifically, uncovering new biomarkers for predicting tDCS neuromodulation effects may be useful in developing criteria for responders to tDCS and tailoring individual rehabilitation therapy programs.

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## 6 APPENDIX

### 6.1 Chapter 3: Additional table

Table 6.1 Occurrence and Incidence of Full and Partial StartReact Responses for LAS Trials Prior to “Go” for Healthy Controls

Subject	Nondominant Arm						Dominant Arm					
	-500 ms		-200 ms		% of SR Response		-500 ms		-200 ms		% of SR Response	
	Full SR	Partial SR	Full SR	Partial SR	Full SR	Partial SR	Full SR	Partial SR	Full SR	Partial SR	Full SR	Partial SR
C#1	0	2	3	1	30	30	4	1	1	3	50	40
C#2	1	1	3	1	40	20	2	0	2	1	40	10
C#3	0	2	0	0	0	20	1	3	2	0	30	30
C#4	4	1	4	1	80	20	1	1	1	1	20	20
C#5	0	0	1	0	10	0	2	1	1	3	30	40
C#6	5	0	2	3	70	30	4	1	5	0	90	10
C#7	4	0	3	0	70	0	1	0	3	1	40	10
C#8	0	2	1	1	10	30	3	1	2	1	50	20
C#9	0	5	2	3	20	80	0	5	1	4	10	90
C#10	5	0	5	0	100	0	2	1	2	1	40	20

Note: There were 10 LAS trials (5 trials per time point) for each arm. The percentage of SR response is the percentage of total number of SR response occurrences at – 500 and – 200 ms divided by the total number of trials.

## 6.2 Chapter 3: Detailed report of results

Additional variables that are not described in the main chapters

1. Reach movement time: Movement time corresponded to the time from the onset to the offset of reach.
2. Normalized anterior peak CoP displacement: Normalized anterior peak CoP displacement were determined by the maximum anterior CoP displacement from the onset of the CoP normalized by reach distance.
3. Anterior peak CoP velocity: Anterior peak CoP velocity was determined as the maximum velocity of the posterior CoP movement.
4. EMG duration: The muscle activation duration corresponded to the time from the onset to the offset of muscle activation. The offsets were taken as the point when the muscle activation falls back to a steady baseline.

### 6.2.1 Effect of LAS timing on task performance

In this section, we examined the effect of LAS timing on biomechanical and muscle activation aspects of APA-reach response for each group.

***Biomechanical aspect:*** The timing of the LAS had a significant effect on the temporal and spatial aspects of APA-reach response in healthy controls but only on temporal aspect in individuals with stroke. In both groups, the average reach onset (Fig 6.1) and APA onset (Fig 6.2) was the latest when the LAS was applied at – 500 ms before the “go” cue among conditions. As the timing of the LAS approached the “go” cue (i.e. – 200 ms and 0 ms), the onset latency of APA and reach gradually decreased as the stimulation timing approached the “go” cue and toward the control reach condition. Similar LAS timing effects were also found on movement time of the reach (Fig 6.3) with gradually decreased as the stimulation timing approached the “go” cue and toward the control reach condition in healthy controls. Although there were significant effects of LAS timing on movement time in the stroke group, we did not find a gradual changes as we found in healthy controls. During the paretic arm reaching, the presence of LAS at – 500 and 0 ms prolonged the reach movement time compared to the control reach condition, and during the nonparetic arm reaching, the presence of LAS at – 200 ms prolonged the movement time compared to when the LAS was at 0 ms and the control reach condition (Fig 6.3). The timing effects of the LAS were found in the APA amplitude (Fig 6.4) and the lag between APA and reach onsets (Fig 6.5) only in healthy controls. In healthy controls, the LAS at – 500 ms was associated with a smaller APA amplitude (in the posterior direction) (Fig 6.4) and longer lag between APA and reach onsets (Fig 6.5) compared to other conditions. As the stimulation timing closer to the

“go” cue, the APA amplitude was gradually increased (Fig 6.4) and the lag was shortened (Fig 6.5). The timing of the LAS also had effects on the trunk and pelvic rotation onsets. The trunk onsets (relative to the reach onset) (Fig 6.6) were the earliest when the LAS was applied at 500 ms before the “go” cue among conditions in healthy controls and during the paretic arm reaching in individuals with stroke. During the nonparetic arm reaching, although the trunk rotation onsets when the LAS was at – 500 ms were not significantly different from that of when the LAS was at – 200 ms and 0 ms, it was significantly earlier than that of the control reach condition (Fig 6.6). For pelvic rotation onsets, there was a main effect of LAS timing across groups with the earliest onset when the LAS at – 500 ms and the latest onset in the control reach condition (Fig 6.7).

There were facilitatory effects with the presentation of the LAS in velocity-related variables. The peak velocity (Fig 6.8) of reach in both groups and the APA velocity (Fig 6.9) in healthy controls were faster when the LAS was at 0 ms compared to other LAS time points and the control reach condition. In the nonparetic arms, the APA peak velocity was faster at time point 0 ms compared to time point – 500 ms and the control reach condition. No facilitatory effect on APA peak velocity was observed during the paretic arm reaching. For the anterior peak CoP velocity (Fig 6.10), in healthy controls, the velocity was faster when LAS was at 0 ms compared to when the LAS was at – 200 ms and the control reach condition but the difference between time point 0 ms and the control reach condition was outside our significant cutoff. In the stroke group, a similar facilitatory effect on the anterior CoP velocity was observed when the LAS was at 0 ms and – 200 ms compared to the control reach condition during the nonparetic arm reaching

and was also observed when the LAS was at 0 ms compared to the control reach condition during the paretic arm reaching.

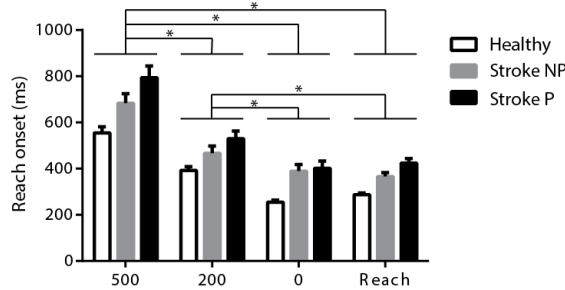


Figure 6.1 Mean ( $\pm$ SE) reach onset across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$

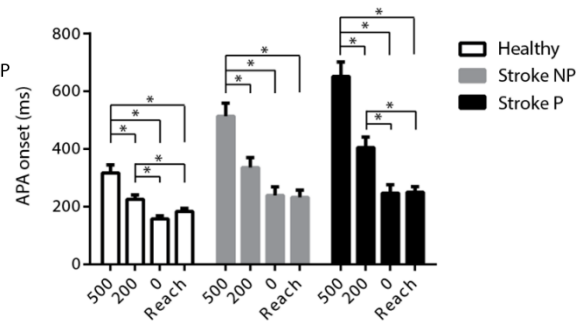


Figure 6.2 Mean ( $\pm$ SE) APA onset across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

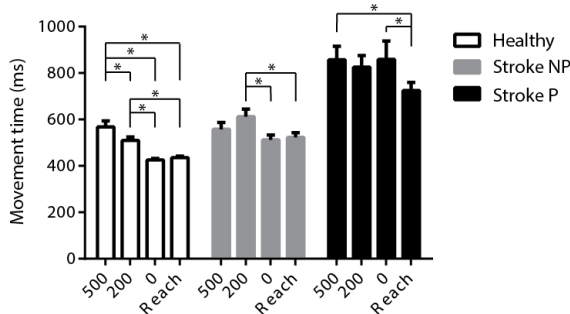


Figure 6.3 Mean ( $\pm$ SE) movement time across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

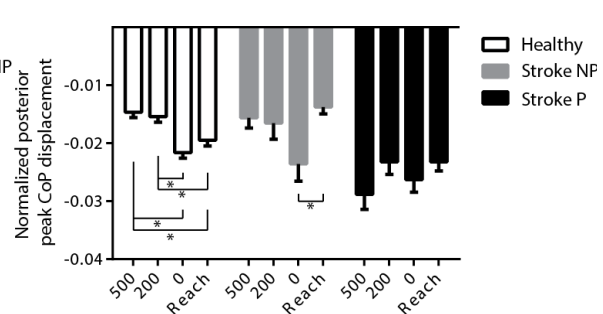


Figure 6.4 Mean ( $\pm$ SE) APA magnitude measured by normalized posterior CoP displacement across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

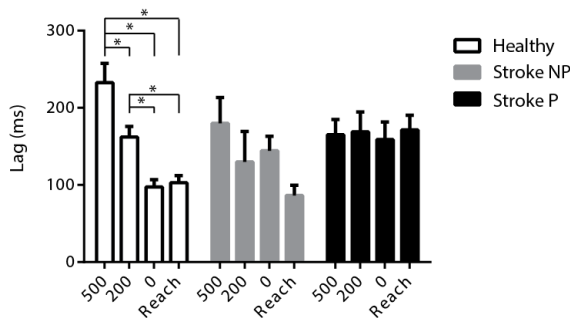


Figure 6.5 Mean ( $\pm$ SE) lag between APA and reach onsets across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $P < 0.05$ .

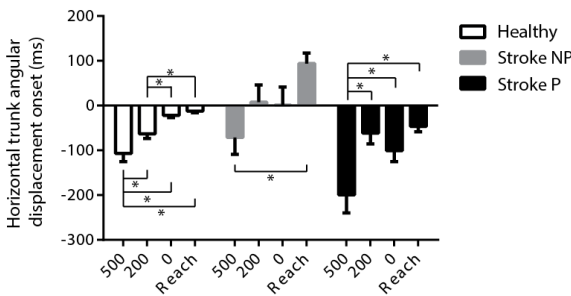


Figure 6.6 Mean ( $\pm$ SE) trunk rotation onsets relative to the reach onsets across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $P < 0.05$ . Note that the negative value in the graphs represents the trunk onset is earlier than reach onset, whereas the positive value represents the trunk onset is later than reach onset.

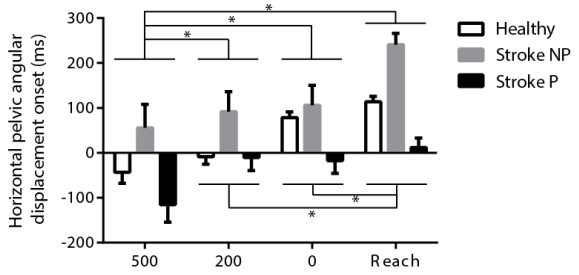


Figure 6.7 Mean ( $\pm$ SE) pelvic rotation onsets relative to the reach onsets across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ . Note that the negative value in the graphs represents the pelvic onset is earlier than reach onset, whereas the positive value represents the pelvic onset is later than reach onset.

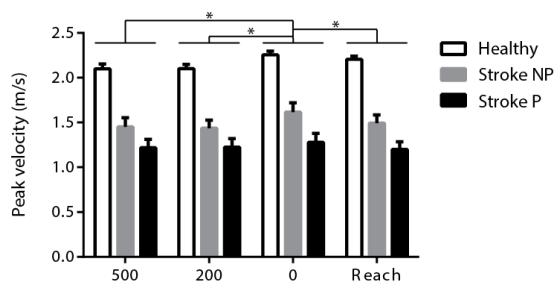


Figure 6.8 Mean ( $\pm$ SE) reach peak velocity across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$

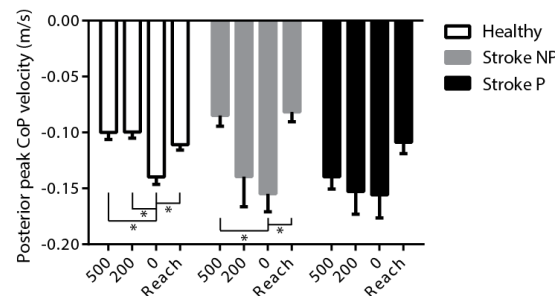


Figure 6.9 Mean ( $\pm$ SE) APA peak velocity as measured by posterior CoP velocity across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$

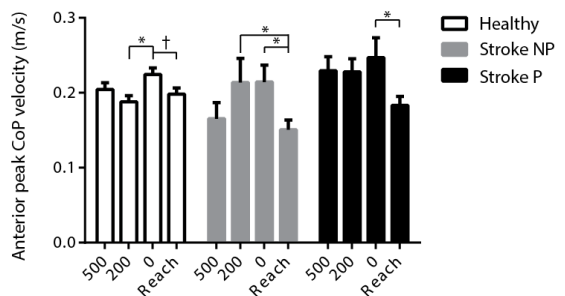


Figure 6.10 Mean ( $\pm$ SE) anterior peak CoP velocity across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$  and †  $p < 0.1$ .

***Muscle activation aspect:*** Significant effects of LAS timing were observed on the muscle activation onsets and duration in AD, onsets in ipsilateral and contralateral TA, and ES. The AD (Fig 6.11) and ES onsets (Fig 6.14) in both groups and the TA onsets (Fig 6.13) in healthy controls had a similar modulation time course with gradual shortness as the LAS timing approached the “go” cue and no difference between LAS time point 0 ms and the control reach condition. The muscle activation duration in AD (Fig 6.12) was longer when the LAS was at – 500 ms compared to LAS time point 0 ms and the control reach condition. Although there was a significant effect of LAS on the ipsilateral TA onset in the stroke group (Fig 6.13A), the onset latency was not significantly gradually shortened as the LAS timing approached the “go” cue. For the contralateral TA onsets in the stroke group (Fig 6.13B), the onset latency was gradually shortened as the LAS timing approached the “go” cue, however, there was significant difference between LAS time point 0 ms and the control reach condition. When the LAS was delivered at the go (i.e. LAS time point 0 ms), the contralateral TA onsets were facilitated as reflected by earlier onsets compared to the control reach condition (Fig 6.13B).

Facilitatory effects with the presentation of LAS were also found on the muscle activation magnitude in AD, TA, and ES. The integrated EMG in AD was greater with the presentation of the LAS regardless of time points compared to the control reach condition in both groups (Fig 6.15). The integrated EMG in TA was greater when the LAS was at 0 ms compared to the control reach condition (Fig 6.16) although the facilitatory effect of different LAS time points was not consistent in both groups. The

integrated EMG in ES (Fig 6.17) was greater when the LAS was at 0 ms compared to when the LAS was at -200 ms and the control reach condition.

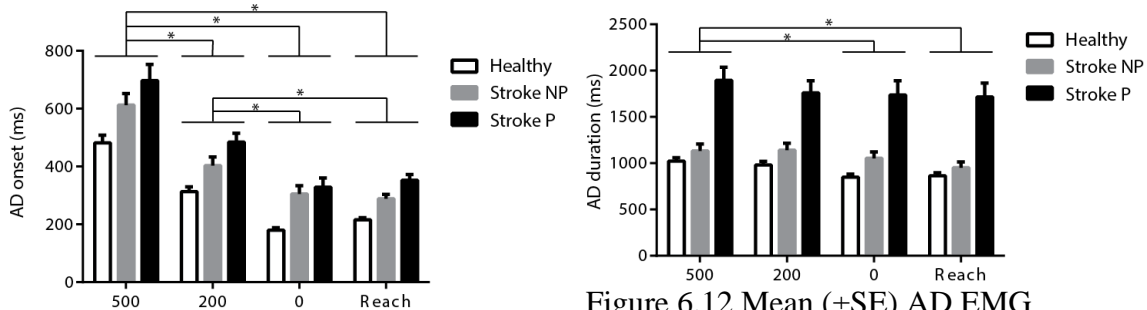


Figure 6.11 Mean ( $\pm$ SE) AD EMG onset across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

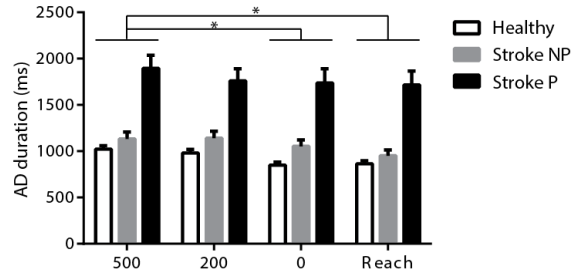


Figure 6.12 Mean ( $\pm$ SE) AD EMG duration across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

(A)

(B)

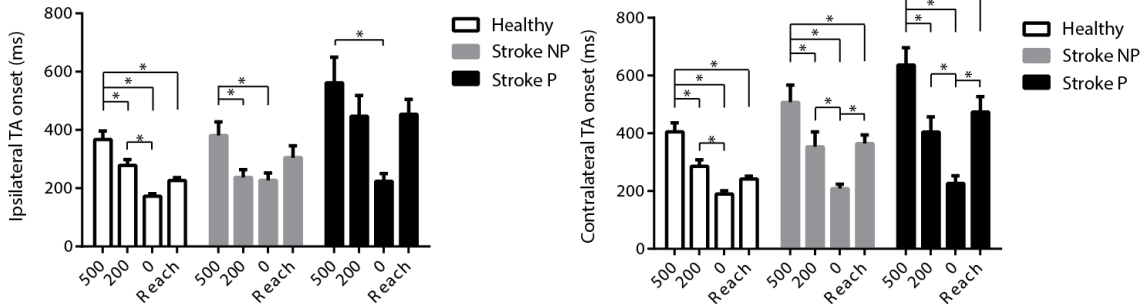


Figure 6.13 Mean ( $\pm$ SE) (A) ipsilateral and (B) contralateral TA EMG onset across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

(A)

(B)

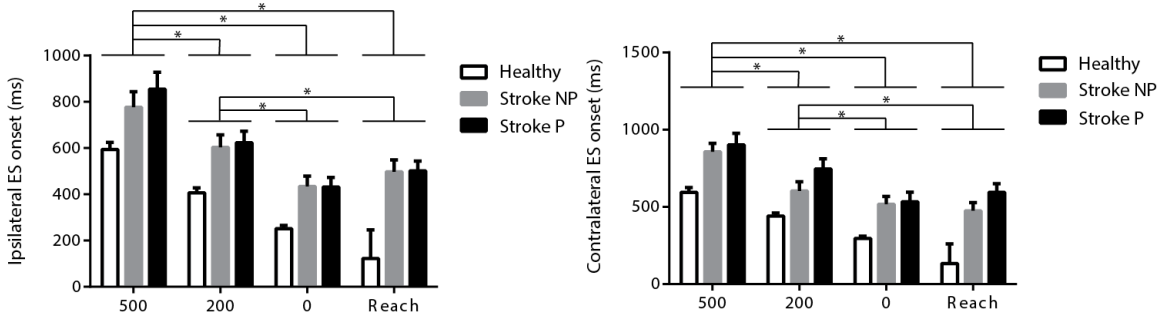


Figure 6.14 Mean ( $\pm$ SE) (A) ipsilateral and (B) contralateral ES EMG onset across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

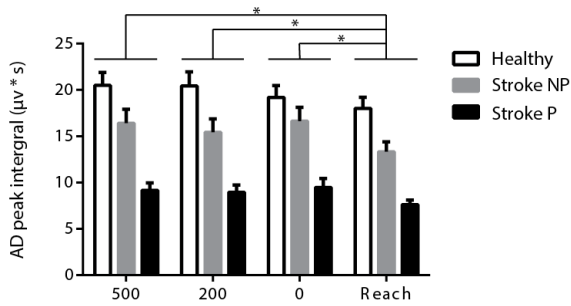


Figure 6.15 Mean ( $\pm$ SE) AD integrated EMG across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

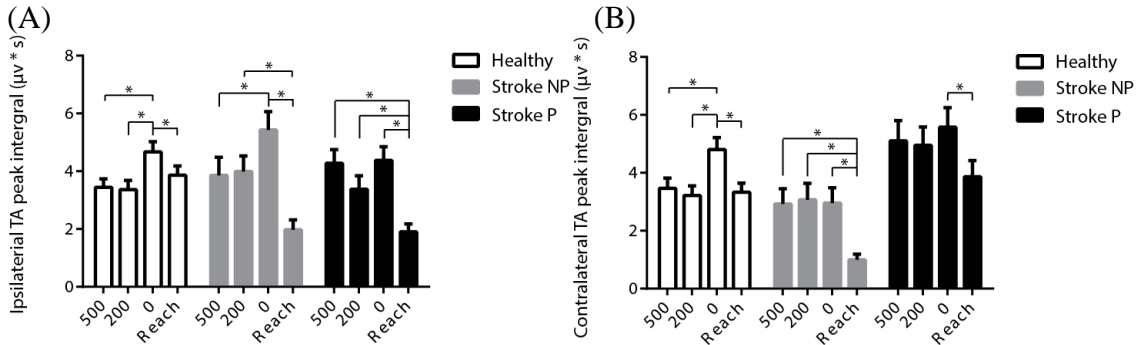


Figure 6.16 Mean ( $\pm$ SE) (A) ipsilateral and (B) contralateral TA integrated EMG across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

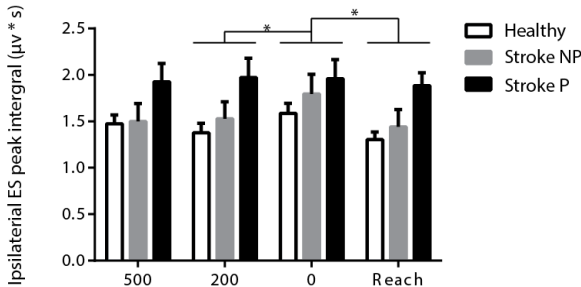


Figure 6.17 Mean ( $\pm$ SE) ipsilateral ES integrated EMG across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

## 6.2.2 Task performance: Comparison between groups and within the stroke group

In this section, we aim at comparing the differences in task performance between healthy and stroke groups and between the paretic and the nonparetic arms within the stroke group, therefore, the same data from the previous section are presented in the figures with reorganization to facilitate comparison.

### 6.2.2.1 *APA-reach performance*

**Biomechanical aspect:** The nonparetic arm demonstrated altered APA-reach performance compared to healthy controls. During the nonparetic arm reaching, later reach onset (Fig 6.18), slower reach peak velocity (Fig 6.19), and later APA onset (Fig 6.20 B) were observed across all LAS conditions.

Not surprisingly, deficits in APA-reach sequence were found during the paretic arm reaching in individuals with stroke compared to healthy controls. General impairments in APA-reach performance during the paretic arm reaching compared to healthy controls were reflected in significantly later reach onset (Fig 6.18), longer reach movement time (Fig 6.21), and slower reach peak velocity (Fig 6.19) across LAS conditions. During the paretic arm reaching, significantly later onsets in APA were observed when the LAS was delivered prior to the go (i.e. – 500 and – 200 time points) and a trend toward later onsets were observed when the LAS was at the “go” cue and the control reach condition in comparison with healthy controls (Fig 6.20A). The lag between APA and reach onsets were longer when the LAS was at 0 ms and the control reach condition (Fig 6.22) although the difference in the control reach condition was outside the significance cutoff. At LAS time point – 500 and – 200 ms, the APA amplitudes were greater during the paretic arm reaching compared to healthy controls (Fig 6.23) although

the difference at LAS time point – 200 ms was outside the significance cutoff. At LAS time point – 500 ms, the APA velocity was greater during the paretic arm reaching compared to healthy controls (Fig 6.24).

Comparing the paretic and the nonparetic arm reaching, later reach onset (Fig 6.18), longer movement time (Fig 6.21), slower reach peak velocity (Fig 6.19), and faster APA velocity (Fig 6.24) were observed across all LAS conditions. In addition, APA amplitudes were greater during the paretic arm reaching at LAS time point – 500, – 200 ms, and the control reach condition in comparison with the nonparetic arm reaching (Fig 6.23).

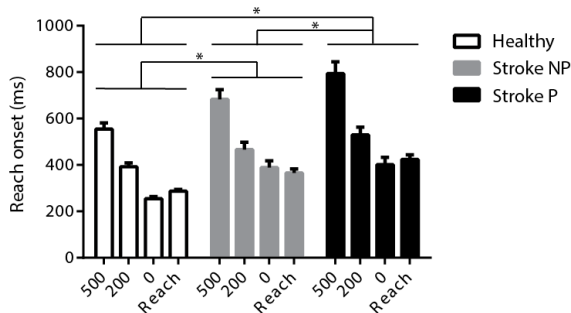


Figure 6.18 Mean ( $\pm$ SE) reach onset across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

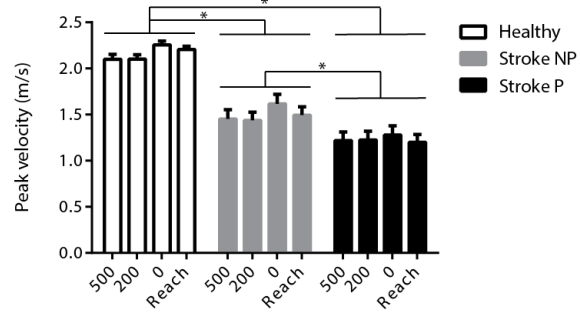


Figure 6.19 Mean ( $\pm$ SE) peak velocity across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

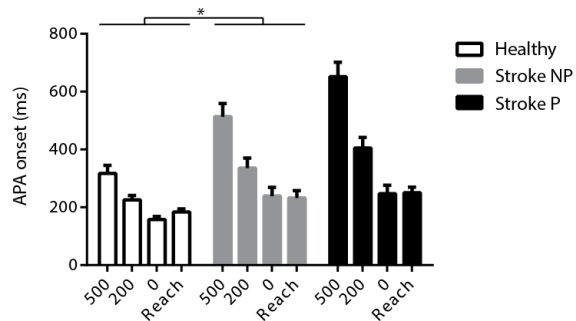
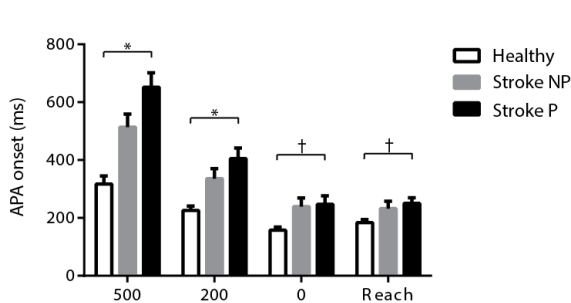


Figure 6.20 Mean ( $\pm$ SE) APA onset across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). Same data are presented in both figures with reorganization to facilitate comparison \*  $p < 0.05$  and †  $p < 0.1$ .

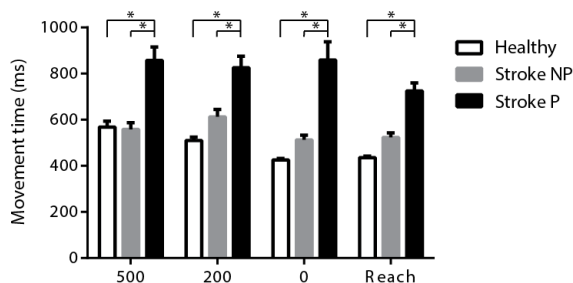


Figure 6.21 Mean ( $\pm$ SE) movement time across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

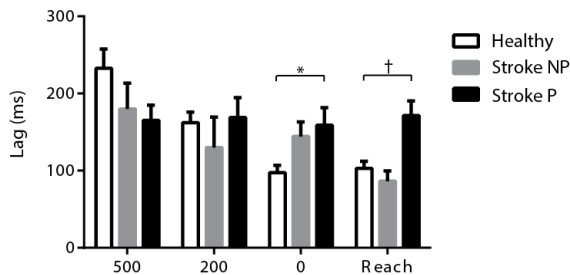


Figure 6.22 Mean ( $\pm$ SE) lag between APA and reach onsets across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$  and †  $p < 0.1$ .

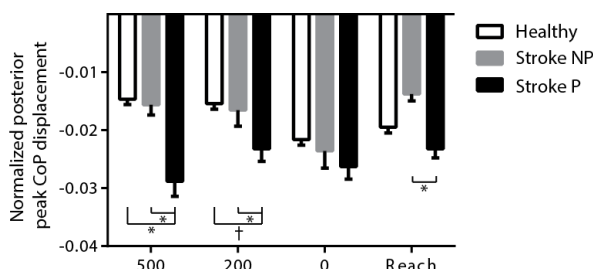


Figure 6.23 Mean ( $\pm$ SE) APA magnitude across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$  and †  $p < 0.1$ .

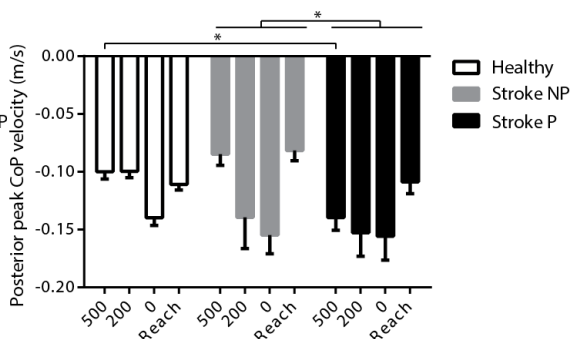


Figure 6.24 Mean ( $\pm$ SE) APA velocity across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

***Muscle activation aspect:*** Impaired muscle activation pattern was found in muscle activation onset, duration, and magnitude during the nonparetic arm reaching compared to healthy controls. Across all LAS conditions, later onset in AD (Fig 6.25) and ES (Fig 6.26) were observed during the nonparetic arm reaching compared to healthy controls. In the control reach condition, later contralateral TA onset (Fig 6.27B), longer contralateral TA duration (Fig 6.29B), and smaller contralateral TA integral (Fig 6.31) during the nonparetic arm reaching compared to healthy controls.

Comparison between the paretic arm reaching and healthy controls found later AD onsets (Fig 6.25), longer AD duration (Fig 6.30), and later ES onset (Fig 6.26) across all LAS conditions. In addition, in the control reach condition, the ipsilateral TA onset (Fig 6.27A) was later during the paretic arm reaching compared to healthy controls. In the control reach condition and at LAS time point – 500 ms, the contralateral TA onset was also later during the paretic arm reaching compared to healthy controls (Fig 6.27B).

Comparison between the paretic and the nonparetic arms reaching movements showed later muscle activation onset in AD (Fig 6.25), longer duration in AD (Fig 6.30), ipsilateral TA duration (Fig 6.28), contralateral TA duration (Fig 6.29A), greater muscle activation in contralateral TA integrated EMG (Fig 6.31), and ES integrated EMG (Fig 6.32) during the paretic arm reaching. There was later ipsilateral TA onsets during the paretic arm reaching at LAS time point – 200 ms and the control reach condition in comparison with the nonparetic arm reaching (Fig 6.27A).

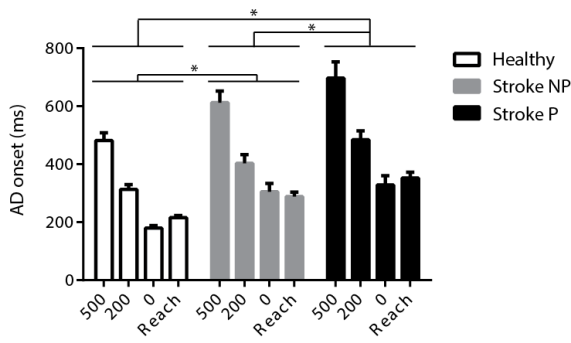


Figure 6.25 Mean ( $\pm$ SE) AD EMG onset across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

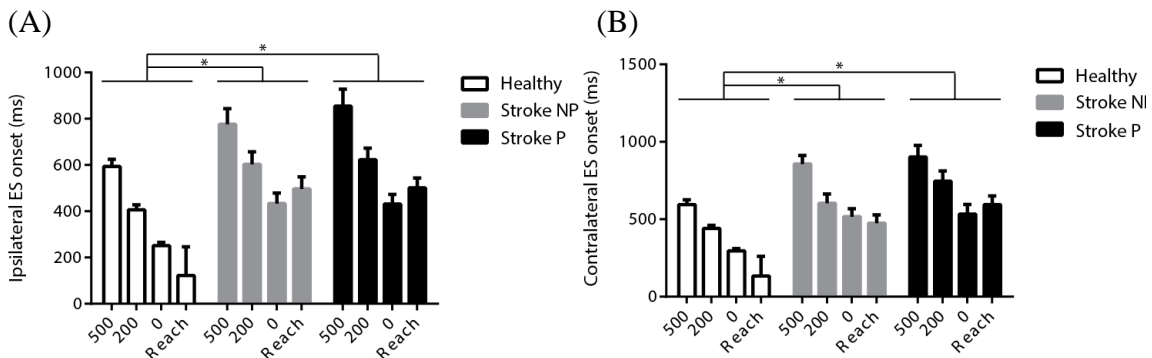


Figure 6.26 Mean ( $\pm$ SE) (A) ipsilateral and (B) contralateral ES EMG onsets across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

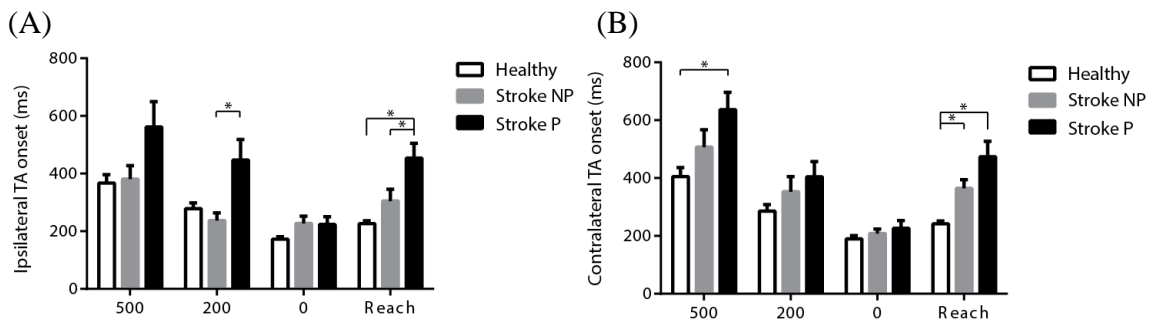


Figure 6.27 Mean ( $\pm$ SE) (A) ipsilateral and (B) contralateral TA EMG onsets across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

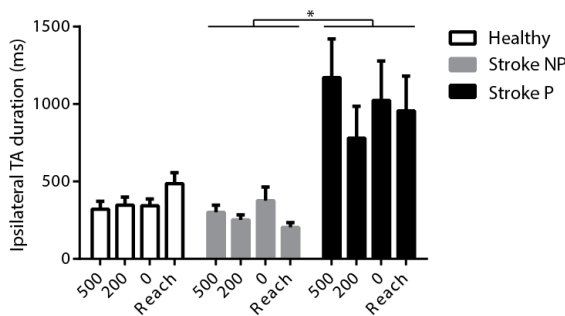


Figure 6.28 Mean ( $\pm$ SE) ipsilateral TA EMG duration across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

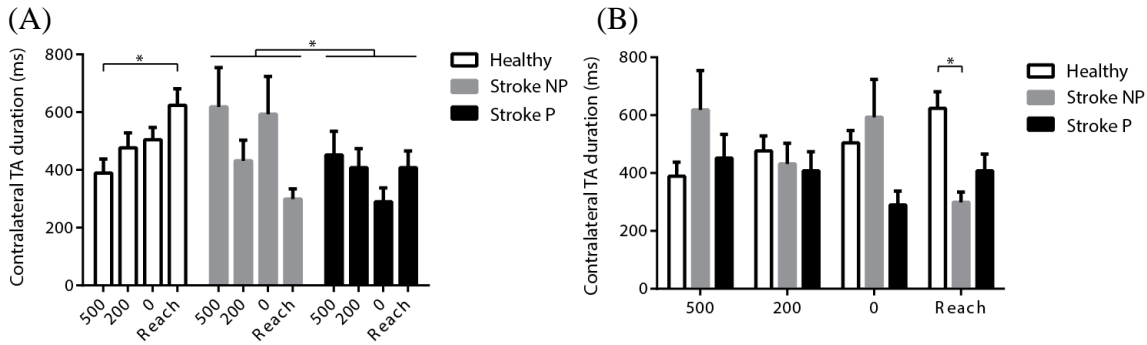


Figure 6.29 Mean ( $\pm$ SE) contralateral TA EMG duration across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

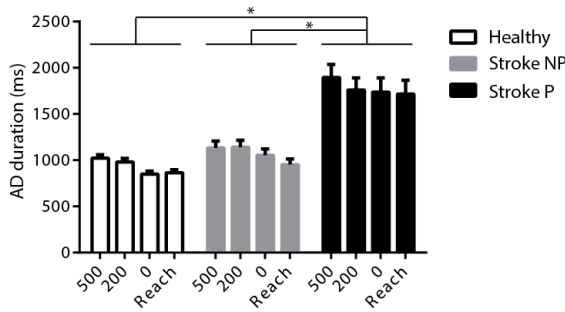


Figure 6.30 Mean ( $\pm$ SE) AD EMG duration across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

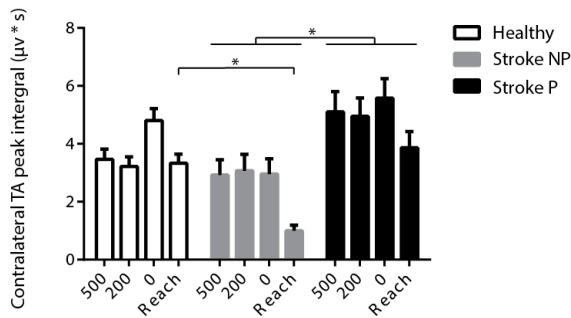


Figure 6.31 Mean ( $\pm$ SE) contralateral TA integrated EMG across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

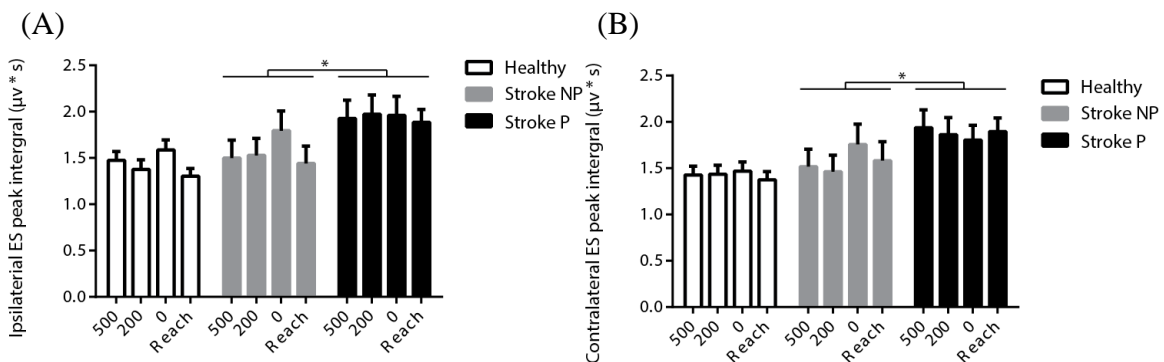


Figure 6.32 Mean ( $\pm$ SE) (A) ipsilateral and (B) contralateral ES integrated EMG across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

### 6.2.2.2 Postural control during reaching execution

**Biomechanical aspect:** Greater pelvic rotation (Fig 6.33), and reduced trunk-pelvic rotation difference (Fig 6.34) were found during the paretic arm reaching compared to the nonparetic arm reaching and healthy controls, indicating that individuals with stroke used a greater “whole body rotation strategy” including trunk and pelvis in order to transport the paretic arm to the target. Comparing between the paretic and nonparetic arm reaching, greater trunk rotation (Fig 6.35) was found during the paretic reaching. There was a significantly reduced trunk rotation (Fig 6.35) during the nonparetic arm reaching compared to healthy controls. Greater anterior CoP displacement (Fig 6.36) and faster anterior CoP peak velocity (Fig 6.37) were found during the paretic arm reaching compared to the nonparetic reaching. Greater anterior CoP displacement (Fig 6.36) was also found during the paretic arm reaching compared to healthy controls when the LAS was at  $-200, 0$  ms, and the control reach condition although the difference was outside the significance cutoff at LAS time point  $0$  ms and the control reach condition.

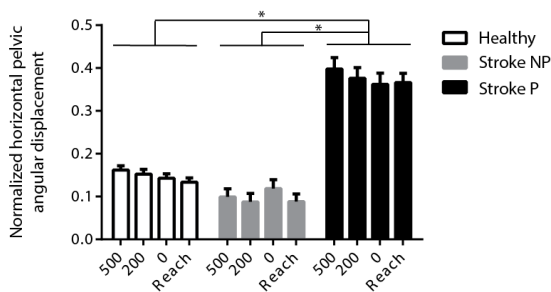


Figure 6.33 Mean ( $\pm$ SE) pelvic rotation across conditions (LAS at  $-500, -200, 0$  ms relative to the go and the control reach condition). \*  $p < 0.05$ .

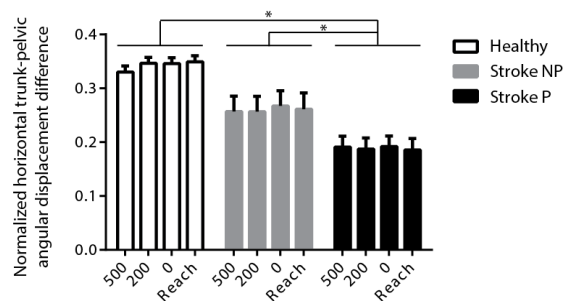


Figure 6.34 Mean ( $\pm$ SE) trunk-pelvic rotation difference across conditions (LAS at  $-500, -200, 0$  ms relative to the go and the control reach condition). \*  $p < 0.05$ .

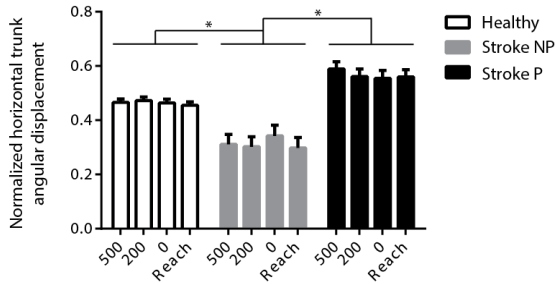


Figure 6.35 Mean ( $\pm$ SE) trunk rotation across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

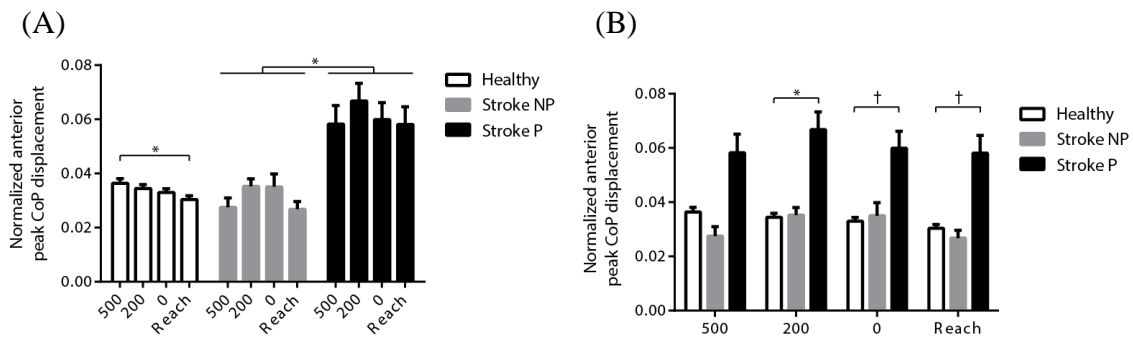


Figure 6.36 Mean ( $\pm$ SE) normalized anterior peak CoP displacement across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$  and †  $p < 0.1$ .

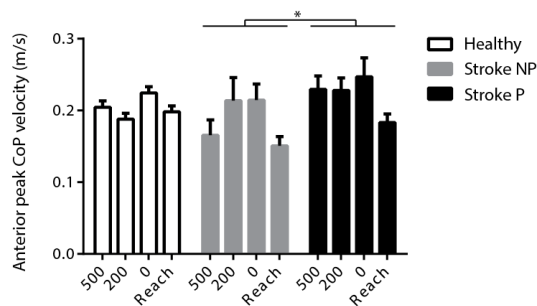


Figure 6.37 Mean ( $\pm$ SE) anterior peak CoP velocity across conditions (LAS at -500, -200, 0 ms relative to the go and the control reach condition). \*  $p < 0.05$ .

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