Behavioral and Neural Correlates of Aging Effects on Temporal Predictive Mechanisms During Speech Production and Limb Movement

Karim Joharikhoatoonabad

Follow this and additional works at: https://scholarcommons.sc.edu/etd

Recommended Citation

This Open Access Dissertation is brought to you by Scholar Commons. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of Scholar Commons. For more information, please contact dillarda@mailbox.sc.edu.
BEHAVIORAL AND NEURAL CORRELATES OF AGING EFFECTS ON TEMPORAL PREDICTIVE MECHANISMS DURING SPEECH PRODUCTION AND LIMB MOVEMENT

by

Karim Joharikhatoonabad

Bachelor of Science
Iran University of Medical Sciences, 2008

Master of Science
Tehran University of Medical Sciences, 2011

Submitted in Partial Fulfillment of the Requirements

For the Degree of Doctor of Philosophy in
Communication Sciences and Disorders
Norman J. Arnold School of Public Health
University of South Carolina

2019

Accepted by:
Roozbeh Behroozmand, Major Professor
Dirk den Ouden, Committee Member
Allen Montgomery, Committee Member
Chris Rorden, Committee Member
Cheryl L. Addy, Vice Provost and Dean of the Graduate School
Dedication

This work is dedicated to my mother and sisters. You have made me stronger, better and more fulfilled than I could have ever imagined. I love you to the moon and back.
Abstract

Existing evidence suggests that the brain facilitates motor responses to temporally predictable sensory inputs by generating more robust predictions about the timing of incoming stimuli to better estimate the next state of movement. In this context, previous studies have shown that motor responses are generated with faster reaction time in response to sensory stimuli with predictable compared to those with unpredictable temporal dynamics. However, our understanding of the underlying behavioral and neural mechanisms of temporal predictive mechanisms during movement production has remained limited by several factors. First, studies regarding temporal predictive mechanisms have mainly examined limb movement as a target modality and less is known about other motor modalities such as speech production. In addition, previous studies have primarily focused on investigating the temporal predictive mechanisms during movement initiation and our understanding of the nature of these mechanisms during movement inhibition has remained elusive. Moreover, most of the previous studies have examined young healthy adults to probe the underlying temporal processing mechanisms during movement and less is known about the effect of normal aging on the behavioral and neural correlates of these mechanisms in older adults.

This dissertation presents the results and discusses the findings of several studies that aimed to bridge these gaps by measuring the behavioral correlates of motor reaction time concurrent with recordings of neural activities using event-related potentials (ERPs) in two groups of younger and older adults while they performed speech and limb
movement initiation and inhibition tasks in responses to temporally predictable and unpredictable sensory stimuli. Findings of these studies revealed that speech and limb motor reaction times are accelerated in response to incoming sensory stimuli with predictable temporal dynamics during both movement initiation and inhibition tasks. In addition, the results revealed that faster reaction times for initiating speech and limb movement were correlated with a significant attenuation of pre-motor ERP activities in response to temporally predictable vs. unpredictable stimuli, suggesting that these components may serve as a neural signature of temporal predictive mechanisms in the motor system. Moreover, the findings showed that ERP activities before limb movement inhibition were attenuated for predictable vs. unpredictable sensory stimuli whereas an opposite pattern of neural activities was observed for speech motor inhibition responses. Furthermore, behavioral findings revealed that older adults were slower than their younger counterparts only during speech motor initiation and inhibition tasks when the stimulus timing was unpredictable, but no such effect was observed during the limb motor reaction time task. Lastly, the results indicated that pre-motor ERP activity prior to the onset of speech, but not limb, movement initiation was significantly larger in older vs. younger adults when stimulus timing was unpredictable, but no difference was observed between the groups in response to temporally predictable sensory stimuli.

Overall, the findings of these studies suggest that common temporal predictive mechanisms may support speech and limb movement initiation in response to sensory stimuli and pre-movement ERPs may be a neural signature of these mechanisms. In contrast, for movement inhibition, findings revealed distinct patterns of premotor ERP activities for speech vs. limb movement, indicating the functional dissociations between
these two modalities, particularly during movement inhibition. Finally, the findings of these studies suggest temporally and modality specific decline in the temporal predictive mechanisms of movement production in older adults and highlight the effect of normal aging on the behavioral and neural correlates of these mechanisms during speech and limb motor reaction time tasks.
Table of Contents

Dedication ................................................................................................................................. iii
Abstract ................................................................................................................................. iv
List of Tables ........................................................................................................................... x
List of Figures .......................................................................................................................... xi
List of Abbreviations ............................................................................................................... xvi
Chapter 1: Introduction .......................................................................................................... 1
  1.1 Temporal Predictive Mechanisms During Speech Production and Limb Movement ................................................................................................................................. 5
  1.2 Neural Correlates of Temporal Predictive Mechanisms in The Motor System .... 6
  1.3 Neural Correlates of Temporal Predictive Mechanisms During Initiation and Inhibition of Movement ................................................................................................. 7
  1.4 Age-related Changes in Temporal Predictive Mechanisms During Movement Initiation and Inhibition ................................................................................................. 9
  1.5 Neural Correlates of Age-related Changes in Temporal Predictive Mechanisms During Speech and Limb Movement Initiation ......................................................... 11

Chapter 2: Temporal Predictive Mechanisms Modulate Motor Reaction Time during Initiation and Inhibition of Speech and Hand Movement ........................................... 14
  2.1 Abstract .......................................................................................................................... 15
  2.2 Introduction .................................................................................................................... 15
  2.3 Material and Methods .................................................................................................... 22
  2.4 Results ........................................................................................................................... 27
  2.5 Discussion ....................................................................................................................... 31
  2.6 Conclusion ...................................................................................................................... 39
3.1 Abstract .................................................................................................................42
3.2 Introduction ............................................................................................................43
3.3 Methods and Materials ..........................................................................................49
3.4 Results ....................................................................................................................53
3.5 Discussion ..............................................................................................................63

Chapter 4: Functional Dissociation of Temporal Processing Mechanisms during Speech Production and Hand Movement: An ERP Study .........................73
4.1 Abstract ..................................................................................................................74
4.2 Introduction ............................................................................................................75
4.3 Methods and Materials ..........................................................................................83
4.4 Results ....................................................................................................................89
4.5 Discussion ..............................................................................................................97

Chapter 5: Effects of Aging on Temporal Predictive Mechanisms of Speech and Hand Motor Reaction Time .................................................................105
5.1 Abstract ................................................................................................................106
5.2 Introduction ............................................................................................................107
5.3 Methods and Materials ..........................................................................................115
5.4 Results ....................................................................................................................117
5.5 Discussion ..............................................................................................................120
5.6 Conclusion ............................................................................................................123

Chapter 6: Behavioral and Neural Correlates of Normal Aging Effects on Motor Preparatory Mechanisms of Speech Production and Limb Movement ........125
6.1 Abstract ................................................................................................................126
6.2 Introduction ............................................................................................................126
6.3 Methods and Materials ..........................................................................................133
6.4 Results ....................................................................................................................138
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.5 Discussion</td>
<td>140</td>
</tr>
<tr>
<td>6.6 Conclusion</td>
<td>155</td>
</tr>
<tr>
<td>Chapter 7: General Discussion and Conclusion</td>
<td>156</td>
</tr>
<tr>
<td>7.1 Behavioral and Neural Correlates of Temporal Predictive Codes in Healthy Young Subjects</td>
<td>157</td>
</tr>
<tr>
<td>7.2 Age-related Changes in Behavioral and Neural Correlates of Temporal Predictive Mechanism During Speech Production and Limb Movement</td>
<td>161</td>
</tr>
<tr>
<td>7.3 The Effects of Response Modality on Motor Reaction Times</td>
<td>164</td>
</tr>
<tr>
<td>7.4 The Effect of Task on Motor Reaction Times</td>
<td>165</td>
</tr>
<tr>
<td>7.5 Conclusion and Future Directions</td>
<td>166</td>
</tr>
<tr>
<td>References</td>
<td>168</td>
</tr>
<tr>
<td>Appendix A: Reprint Permission for Papers in Chapters 2&amp;4</td>
<td>189</td>
</tr>
<tr>
<td>Appendix B: Reprint License for Paper in Chapter 3</td>
<td>190</td>
</tr>
<tr>
<td>Appendix C: Reprint License for Paper in Chapter 5</td>
<td>191</td>
</tr>
<tr>
<td>Appendix D: Reprint License for Paper in Chapter 6</td>
<td>192</td>
</tr>
</tbody>
</table>
List of Tables

Table 2.1 The Means and Standard Deviations of Reaction Times During Predictable and Unpredictable Conditions for Speech and Hand Modalities and Movement Initiation and Inhibition Tasks...........................................................................................................27

Table 3.1 The Means and Standard Deviations of Speech and Hand Motor Reaction Times for Predictable and Unpredictable Conditions ..............................................54

Table 4.1 The Means and Standard Deviations of Motor Reaction Times for Two Timing (Predictable vs. Unpredictable) Conditions and Two Tasks (Initiation vs. Cessation), Separately for Speech and Hand Modalities .................................................90

Table 5.1 The Means and Standard Deviations of Reaction Times for Younger and Older Adults During Initiation and Inhibition of Speech Production and Hand Movement for Predictable and Unpredictable Conditions.................................118
List of Figures

Figure 2.1 Experimental Design for Speech and Hand Motor Reaction Time Tasks During Predictable and Unpredictable Blocks ........................................ 25

Figure 2.2 Comparison Between Movement Reaction Times During Predictable vs. Unpredictable Conditions .......................................................... 29

Figure 2.3 Results of The Correlation Analysis for Hand and Speech Movement Initiation and Inhibition Reaction Times During Predictable Condition .......................................................... 30

Figure 2.4 Results of The Correlation Analysis for Hand and Speech Movement Initiation and Inhibition Reaction Times During Unpredictable Condition .......................................................... 30

Figure 3.1 Experimental Design of The Motor Reaction Time Task for Temporally Predictable and Unpredictable Blocks ............................................... 51

Figure 3.2 The Temporal Profile of ERPs and Their Topographical Distribution Maps in Response to hand movement onset ........................................... 57

Figure 3.3 The Bar Plot Representation of Grand-average Premotor ERP Responses to Hand Movement Onset for Temporally Predictable vs. Unpredictable Condition ......................................................... 58

Figure 3.4 The Temporal Profile of ERPs and Their Topographical Distribution Maps in Response to Speech Movement Onset ........................................ 60

Figure 3.5 The Bar Plot Representation of Grand-average Premotor ERP Responses to Speech Movement Onset for Temporally Predictable vs. Unpredictable Condition ......................................................... 61

Figure 3.6 Temporal Profiles and Topographical Plots of The Correlation Between ERP Amplitudes and Behavioral Reaction Times for Hand Movement Initiation ................................................................. 62

Figure 3.7 Temporal Profiles and Topographical Plots of The Correlation Between ERP Amplitudes and Behavioral Reaction Times for Hand Movement Initiation ................................................................. 64
Figure 6.4 Profiles of The Mean Amplitude of ERPs Across Older and Younger Adults in 10 Different Time Windows Before The Onset of Speech and Limb Movement in Response to Temporally Predictable and Unpredictable Stimuli .................................................................143
## List of Abbreviation

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>ERD</td>
<td>Event-related Desynchronization</td>
</tr>
<tr>
<td>FP</td>
<td>Foreperiod</td>
</tr>
<tr>
<td>ICA</td>
<td>Independent Component Analysis</td>
</tr>
<tr>
<td>IPC</td>
<td>Left Inferior Parietal Cortex</td>
</tr>
<tr>
<td>ISI</td>
<td>Inter-stimulus Interval</td>
</tr>
<tr>
<td>MPC</td>
<td>Medial Premotor Cortex</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s Disease</td>
</tr>
<tr>
<td>rDLPFC</td>
<td>right Dorsolateral Prefrontal Cortex</td>
</tr>
<tr>
<td>Rm-ANOVA</td>
<td>Repeated-measures Analysis of Variance</td>
</tr>
<tr>
<td>SMA</td>
<td>Supplementary Motor Area</td>
</tr>
<tr>
<td>STN</td>
<td>Subthalamic Nucleus</td>
</tr>
<tr>
<td>VLPFC</td>
<td>Ventrolateral Prefrontal Cortex</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction
The ability to generate complex and adaptable movements is an important function of the human nervous system that enables us to interact with the environment to achieve behaviorally relevant goals in the external world (e.g. grabbing a cup of coffee, driving a car, hitting a tennis ball or speaking to a friend). However, the underlying neural and behavioral mechanisms of movement production and control are not fully understood.

Recent models of movement production and control suggest that the brain can internally simulate the behavior of the motor system during planning, execution and control of the movement (Wolpert, Diedrichsen, & Flanagan, 2011; Wolpert & Flanagan, 2001). According to these models, the brain can internally stimulate the behavior of the motor system through learning the intrinsic properties of the motor commands and predicting the sensory consequences of our own self-produced actions. In this context, the internal forward model theory (Wolpert, Diedrichsen, & Flanagan, 2011; Wolpert & Flanagan, 2001) has proposed that an internal forward model learns the association between the efference copies of the motor commands and their sensory consequences in order to fine tune and control motor commands during movement production.

It has been hypothesized that the outcome of this process results in establishing a predictive code that estimates the current and future states of the system in order to make necessary adjustments when motor error occurs during movement. Previous studies on limb (Flanagan, Vetter, Johansson, & Wolpert, 2003; Wolpert, Ghahramani, & Flanagan, 2001) and speech motor control (Guenther, Ghosh, & Tourville, 2006; Hickok & Poeppel, 2004, 2007; Houde & Nagarajan, 2011) have suggested that these mechanisms follow the principles of the internal forward model theory.
An important question regarding predictive codes in the motor system is how the brain can establish temporal predictions about the timing of upcoming movements in response to sensory stimuli. Previous studies on limb movement (Bard et al., 1992; Blakemore, Wolpert, & Frith, 1998; Johansson & Westling, 1988; Witney, Goodbody, & Wolpert, 1999) and speech (Behroozmand, Liu, & Larson, 2011; Behroozmand, Sangtian, Korzyukov, & Larson, 2016; Chen, Chen, Liu, Huang, & Liu, 2012; Kotz & Schmidt-Kassow, 2015), demonstrated that when sensory stimuli arise from self-produced motor actions, the internal forward model predicts the temporal relationships between motor commands and their sensory consequences. Findings of these studies have suggested that temporally predictable patterns can be learned by the internal forward model and subsequently modulate perceptual sensations arising from self-generated motor actions. In addition, studies have shown that the neural correlates of motor movement are differentially modulated by predictable vs. with unpredictable stimuli (Alegre et al., 2003; Bevan et al., 1965; Koppe et al., 2014; Schwartze, Rothermich, & Kotz, 2012), indicating that the internal predictive mechanisms are affected by the temporal dynamics of environmental sensory cues.

A recent development in feedforward theory (Schubotz, 2007) provides more insights about the temporal predictive mechanism in the motor system. According to this account, the human motor cortex, particularly the premotor region, is not only responsible for temporal processing of movement production, but also plays a crucial role in extracting external timing information and incorporating this into motor commands. According to this account, the motor system can extract and establish temporal predictions about timing of upcoming sensory events and these predictions are more
robust and accurate if the temporal aspects of sensory stimuli are predictable. In this context, previous studies showed that motor reaction times are faster in response to temporally predictable sensory stimuli as compared to unpredictable indicating that externally predictable timing information can enhance temporal predictions about when to initiate movement in response to sensory stimuli and subsequently facilitate motor planning and execution.

However, our understanding about temporal predictive mechanisms in the motor system is limited by several factors. First, studies regarding temporal predictive mechanisms in the motor system have been primarily focused on limb movement (Coull et al., 2016; Koppe et al., 2014; Li et al., 2005; Mattes & Ulrich, 1997; Vallesi, McIntosh, Shallice, et al., 2009; Vallesi, McIntosh, & Stuss, 2009) and less is known about more complex motor modalities such as speech production. In addition, previous studies have mainly examined the predictive mechanisms during movement initiation (Bertelson & Boons, 1960; Bevan et al., 1965; Coull et al., 2016; Karlin, 1959; Klemmer, 1956; Koppe et al., 2014; Vallesi, McIntosh, Shallice, et al., 2009), and it is still not clear to what extent the inhibition of ongoing movement shares common predictive mechanisms with movement initiation. Note, movement inhibition and cessation will be used interchangeably throughout this dissertation and both terms refer to stopping ongoing movement. Finally, temporal predictive mechanisms have been largely examined in young healthy subjects (Coull et al., 2016; Koppe et al., 2014; Li et al., 2005; Mattes & Ulrich, 1997; Vallesi, McIntosh, Shallice, et al., 2009) and it is not fully understood how these mechanisms would be modulated by normal aging. The remainder of the
introduction will focus on the current status and gaps regarding neural and behavioral correlates of temporal predictive mechanisms in the motor system.

1.1 Temporal Predictive Mechanisms During Speech Production and Limb Movement

The motor system generates movements with extremely fine temporal precision in response to behaviorally-relevant sensory stimuli. In previous studies, the underlying mechanisms of temporal processing during movement have been investigated using the foreperiod (FP) paradigm in which the time interval between a warning and an imperative signal was randomly manipulated while human subjects performed a motor response reaction time task (Drazin, 1961; Karlin, 1959; Klemmer, 1956; Niemi & Naatanen, 1981). Results of these studies have indicated that the mean reaction time of motor responses was significantly shorter (i.e., faster movements) for fixed-duration (predictable) compared with variable-duration (unpredictable) FPs, suggesting that the pattern of temporal regularity in FPs can modulate reaction time for motor responses during movement initiation (Bevan, Hardesty, & Avant, 1965; Mattes & Ulrich, 1997; Niemi & Naatanen, 1981; Vallesi, McIntosh, Shallice, & Stuss, 2009).

The findings of these studies indicated that predictable timing information can lead to more robust and accurate temporal predictive codes for limb movement. However, the behavioral studies regarding temporal predictive codes mainly focused on limb movement and less is known about these mechanisms in speech production. Previous studies have demonstrated the neuroanatomical overlap between speech and limb movement systems, particularly in frontal and fronto-parietal regions (Gentilucci,
indicating that speech and limb movement may share common neural mechanisms. However, it is not clear to what extent speech and limb movement are subserved by common temporal predictive mechanisms or if they are driven by modality-specific temporal predictive mechanisms. Finally, most previous research has examined temporal predictive mechanisms during movement initiation, and it is relatively unclear if movement initiation and inhibition shares common temporal mechanisms. In chapter 2, a study is presented to investigate the behavioral correlates of temporal predictive mechanisms during initiation and inhibition of speech and limb movement in healthy young subjects.

1.2 Neural Correlates of Temporal Predictive Mechanisms in The Motor System

In line with behavioral studies into temporal predictive mechanisms in the motor system, neuroimaging studies have also provided new insights into the temporal mechanism of movement by showing functional disassociation between brain regions involved in processing sensory stimuli with predictable vs. unpredictable temporal patterns (Thickbroom et al. 2000; Vallesi et al. 2007; Vallesi et al. 2009). These studies found stronger neural activation in the supplementary motor area (SMA), (SMA) (Thickbroom et al. 2000), as well as the right dorsolateral prefrontal cortex (DLFPC) (Vallesi et al. 2007; Vallesi et al. 2009) for limb movements when timing information was unpredictable. In contrast, neural activities in the left inferior parietal cortex (IPC) were reported to be strongly activated for movements in response to temporally-predictable vs. unpredictable stimuli (Coull et al. 2016).
Although stimulus temporal predictability was shown to modulate neural activation after the onset of movement, a number of other studies have reported that pre-movement neural activation is also modulated in response to temporally predictable vs. unpredictable sensory stimuli (Alegre et al. 2003; Kühn et al. 2004; Baker et al. 2012). Electroencephalography (EEG) recordings in humans have demonstrated that pre-movement neural activities are elicited up to two seconds before the onset of the motor action and were found to be stronger in scalp electrodes over the bilateral frontal areas (Baker et al. 2012). In addition, event-related desynchronization (ERD) of beta band (13-30 Hz) activities was reported in contralateral central electrodes prior to the onset of hand motor responses to temporally predictable sensory stimuli (Alegre et al. 2003). The findings of these studies have suggested that pre-motor ERPs before onset of the limb movement may be a neural marker of temporal predictive mechanisms in the hand motor systems. These studies have mainly focused on the limb movement initiation and it is not clear if common neural mechanisms subserve temporal predictive processes for speech and limb movement initiation. In chapter 3, a study is presented to examine the ERP correlates of temporal predictive mechanisms during speech and limb movement initiation in healthy young subjects.

1.3 Neural Correlates of Temporal Predictive Mechanisms During Initiation and Inhibition of Movement

As mentioned above, temporally predictable sensory stimuli can accelerate movement initiation by generating more precise prediction about when to initiate movement. However, few studies have examined the effect of temporal aspects of sensory stimuli on movement inhibition reaction time (Berchicci et al., 2015; Li et al.,
2005). While some studies have found that movement inhibition is not sensitive to the predictability of sensory stimuli (Logan & Burkell, 1986; Ramautar et al., 2004), others indicated that temporally predictable sensory stimuli can accelerate movement inhibition compared to unpredictable stimuli (Berchicci et al., 2015; Li et al., 2005). Nevertheless, it is relatively unclear whether temporal processing of movement initiation and inhibition share common mechanisms.

Previous neuroimaging studies have mainly probed the neural correlates of temporal predictive mechanisms during movement initiation. Although these mechanisms have not been widely studied during inhibition of ongoing movement, distinct patterns of brain activations were observed in response to predictable vs. unpredictable sensory stimuli during inhibition button press tasks, similar to findings for movement initiation (Leunissen, Coxon, & Swinnen, 2016; Vink et al., 2005). These studies have revealed that the striatum was more strongly activated as the temporal predictability of the inhibitory cue signals was increased (Vink et al., 2005). In addition, it has also been shown that when subjects performed limb movement inhibition during a stop signal task, two distinct areas in the basal ganglia were differentially activated in response to frequent vs. infrequent stop trails (Leunissen et al., 2016). Findings of this latter study showed that the areas within the subthalamic nucleus (STN) and anterior striatum exhibited greater activations when stop signals were presented infrequently (unpredictable), whereas greater activations were observed in the caudate nucleus when stop signals followed a frequent (predictable) pattern. However, these studies mainly focused on limb movement inhibition and it is unclear if common underlying neural mechanisms are involved in temporal predictive mechanisms during speech and limb movement inhibition. In
addition, the neural correlates of temporal predictive mechanisms have been mainly examined during hand movement initiation and/or inhibition and it is an open question whether such mechanisms are driven by common or functionally dissociated neural substrates during tasks involving speech initiation and inhibition. In the chapter 4, a study is presented to investigate the neural correlates of temporal predictive mechanisms during initiation and inhibition of speech and limb movement in healthy young subjects.

1.4 Age-related Changes in Temporal Predictive Mechanisms During Movement Initiation and Inhibition

Temporal predictive mechanisms in the motor system have been mainly studied in younger adults (Behroozmand, Sangtian, et al., 2016b; Bertelson & Boons, 1960; Karlin, 1959b; Koppe et al., 2014; Mattes & Ulrich, 1997b; Vallesi, McIntosh, Shallice, et al., 2009), and the effect of normal aging on these mechanisms remains relatively unclear.

Previous studies have found that as individuals age, they show increasing difficulties in processing of temporal information at sensory (Balci, Meck, Moore, & Brunner, 2009; Craik & Hay, 1999) and motor levels (Fozard, Vercruyssen, Reynolds, Hancock, & Quilter, 1994; Levin, Fujiyama, Boisgontier, Swinnen, & Summers, 2014; Munoz, Broughton, Goldring, & Armstrong, 1998). Older adults are slower than younger adults during motor reaction time tasks (Singleton, 1955; Vallesi, McIntosh, & Stuss, 2009). This slower reaction time in older adults may be attributed to a slower central processing, which can subsequently decelerate movement production reaction time (Jerry & Stelmach, 1998).
Alternatively, this effect can also be accounted for by a specific deficit in temporal information processing in older adults (Block, Zakay, & Hancock, 1998; Craik & Hay, 1999; Espinosa-Fernández, Miró, Cano, & Buela-Casal, 2003; Zanto et al., 2011). Older adults have also been reported to make more errors than younger adults during the performance of time perception-related tasks (Espinosa-Fernández et al., 2003). Specifically, older adults are shown to overestimate temporal intervals, suggesting difficulty in processing temporal information for sensory stimuli (Block et al., 1998). It has been suggested that motor timing and time perception are subserved by common neural networks in motor cortex (Schubotz, Friederici, & Von Cramon, 2000), so that slower reaction times in older adults might be due to a general decline in temporal processing for movement production.

While studies have shown abnormal temporal processing in older individuals, it is not fully understood how aging can affect temporal predictive coding mechanisms in the motor system. It has been demonstrated that older adults are significantly slower than younger adults in limb movement initiation during both fixed and variable FPs, suggesting age-related decline in temporal predictive code mechanisms in the limb motor system (Vallesi, McIntosh, & Stuss, 2009). Moreover, older adults have been shown to fail to use explicit temporal cues to accelerate limb movement reaction time during short FPs, while younger subjects responded faster than older adults and used temporal cues to facilitate limb movement initiation (Zanto et al., 2011). In contrast, a recent study (Chauvin, Gillebert, Rohenkohl, Humphreys, & Nobre, 2016) has found that both older and younger adults can benefit from explicit temporal cues during short FPs to accelerate limb movement reaction times. Therefore, findings on temporal predictive mechanisms in
older adults do not conform to a consistent framework across different studies and it is not fully understood how aging may influence temporal processing mechanisms in the human motor system. In chapter 5, a study is presented to examine the behavioral aspects of age-related changes in temporal predictive mechanisms during initiation and inhibition of speech and limb movement.

1.5 Neural Correlates of Age-related Changes in Temporal Predictive Mechanisms During Speech and Limb Movement Initiation

Normal aging is associated with functional decline in the temporal processing mechanisms of movement production, as indexed by age-related slowness of motor reaction time in response to externally presented sensory stimuli (Bherer and Belleville 2004; Sterr and Dean 2008; Balci et al. 2009; Seidler et al. 2010; Diersch et al. 2016). Such reduced capacity for motor timing processing has been suggested to result from declined internal temporal predictive mechanisms in older adults (Vieweg et al. 2015), and their reduced accuracy in predicting the timing of movement sequences during action occlusion tasks (Diersch et al. 2012; Diersch et al. 2013; Wolpe et al. 2016).

Age-related decline in the neural mechanisms of temporal predictive coding was characterized by decreased power of the alpha and increased power of the beta band neural oscillations in older adults during the planning phase of limb movement (Zanto et al. 2011; Vaden et al. 2012; Deiber et al. 2013). In other studies, neural deficits during the planning phase of limb movement in older adults were characterized by age-related increase in the amplitude of ERPs prior to the onset of movement, which was associated
with the slowness of motor reaction time responses (Haaland et al. 1993; Yan et al. 1998; Berchicci et al. 2012). In addition, neuroimaging studies have demonstrated that older adults have difficulties in incorporating temporal information from external sensory stimuli for motor timing coordination and exhibit slower reaction times compared with their younger adult counterparts (Vallesi et al. 2009; Zanto et al. 2011). The neural substrates of such age-related changes have been identified by showing that areas within the right dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) were less activated in older vs. younger adults during movement initiation in response to temporally unpredictable sensory stimuli (Vallesi et al. 2009). These findings indicate an age-related selective deterioration in sensory processing and motor timing coordination in response to stimuli with unpredictable temporal dynamics.

Previous studies mainly examined neural correlates of age-related changes in temporal predictive mechanisms during limb movement and it is not clear how normal aging would affect the underlying neural correlates of these mechanisms during speech production. In chapter 6, a study is presented to examine the neural correlates of age-related changes in temporal predictive mechanisms during speech and limb movement initiation.

Before proceeding to the next chapter, it is noteworthy to clarify the definition and description of a few technical terms, which will be used in all five studies presented in this dissertation. First, the term “movement inhibition” refers to processes that underlie stopping an ongoing movement or movement cessation, which is different from inhibiting an intended movement as discussed in previous studies (Berchicci et al., 2015; Morein-Zamir et al., 2007). More specifically, ”movement inhibition” in previous studies...
refers to the process of withholding a planned motor action in response to a “No-Go” signal as compared to experimental paradigms that involve stopping an ongoing movement in studies presented in this dissertation. Therefore, to avoid any confusion, it is noteworthy to mention that the terms “inhibition” and “cessation” of movement are being used interchangelable in this disseration and both terms refer to the process of stopping an ongoing movement. Second, “speech” and “hand” movement in this disseration refer tasks involving vocalization of a speech vowel sound and pressing a button using the index finger of the dominant hand, respectively. In addition, it is also noteworth to mention that the terms “limb” and “hand” movement are being used interchangebley throughout this disseration and both terms refer to the button press task.
Chapter 2

Temporal Predictive Mechanisms Modulate Motor Reaction Time during Initiation and Inhibition of Speech and Hand Movement

2.1 Abstract

Skilled movement is mediated by motor commands executed with extremely fine temporal precision. The question of how the brain incorporates temporal information to perform motor actions has remained unanswered. This study investigated the effect of stimulus temporal predictability on response timing of speech and hand movement. Subjects perform a randomized vowel vocalization or button press task in two counterbalanced blocks in response to temporally-predictable and unpredictable visual cues. Results indicated that speech and hand reaction time was decreased for predictable compared with unpredictable stimuli. This finding suggests that a temporal predictive code is established to capture temporal dynamics of sensory cues in order to produce faster movements in responses to predictable stimuli. In addition, results revealed a main effect of modality, indicating faster hand movement compared with speech. We suggest that this effect is accounted for by the inherent complexity of speech production compared with hand movement. Lastly, we found that movement inhibition was faster than initiation for both hand and speech, suggesting that movement initiation requires a longer processing time to coordinate activities across multiple regions in the brain. These findings provide new insights into the mechanisms of temporal information processing during initiation and inhibition of speech and hand movement.

2.2 Introduction

The ability to produce movement is a key function that subserves many different aspects of behavior. Humans produce a large category of movements to reach a target or accomplish the goal of a behaviorally-relevant task (e.g. grabbing a cup of coffee, driving a car, hitting a tennis ball or speaking to a friend). The question of how the brain initiates
and controls movement has been debated for decades and our understanding about its underlying mechanisms has remained relatively unclear.

A functionally significant aspect of the motor system is to drive movements that are being generated with extremely fine temporal precision in response to behaviorally-relevant sensory stimuli. In previous studies, the underlying mechanisms of temporal information processing during movement have been investigated using the foreperiod (FP) paradigm in which the time interval between a warning and an imperative signal was randomly manipulated while human subjects performed a motor response reaction time task (Drazin, 1961; Karlin, 1959; Klemmer, 1956; Niemi & Naatanen, 1981). Results of these studies have indicated that the mean reaction time of motor responses was significantly shorter (i.e., faster movements) for fixed-duration compared with variable-duration FPs, suggesting that the pattern of temporal regularity in FPs can modulate reaction time for motor responses during movement initiation (Bertelson & Boons, 1960). A consistent effect has also been reported by other studies using a different experimental paradigm in which the inter-stimulus interval (ISI) was manipulated during motor response reaction time tasks (Bevan, Hardesty, & Avant, 1965; Mattes & Ulrich, 1997; Niemi & Naatanen, 1981; Vallesi, McIntosh, Shallice, & Stuss, 2009).

Findings of these studies revealed that the reaction time for initiating hand motor responses was significantly shorter and movements were performed with a greater temporal precision in response to fixed-ISI (predictable) compared with variable (unpredictable) sensory stimuli.

The earlier models of information processing theory (Karlin, 1959) have proposed that these observed effects are accounted for by a more accurate estimation of conditional
probability and an increased likelihood of anticipating the timing of sensory cues for fixed-duration (temporally-regular) FPs or predictable ISIs, which can lead to movements with shorter reaction times. According to this model, a higher level of readiness for the imperative signal can be established for fixed-duration (regular) FPs or predictable ISIs, whereas variable-duration (irregular) FPs or unpredictable ISIs increase the temporal uncertainty of the imperative signal, leading to longer motor response reaction times during movement initiation. Moreover, it has also been established that factors such as physical properties of the warning and imperative signals (e.g., loudness of the auditory or brightness of visual cues) (Niemi & Lehtonen, 1982; Sanders & Wertheim, 1973) and temporal resolution of FPs (Karlin, 1959) can modulate motor response reaction times during hand movement initiation.

Recent models of movement control have proposed that the brain can internally simulate the behavior of the motor system during planning, execution and control of movement (Miall & Wolpert, 1996; Wolpert, 1997). These internal simulations are hypothesized to form the bases of skilled motor behavior through learning the intrinsic properties of the motor system and predicting the sensory consequences of our own self-produced actions.

In this context, the internal forward model theory (Wolpert, Diedrichsen, & Flanagan, 2011; Wolpert & Flanagan, 2001) has proposed that an internal forward model learns the association between the efference copies of the motor commands and their sensory consequences in order to fine tune and control motor commands during movement production. It has been hypothesized that the outcome of this process results in establishing a predictive code that estimates the current and future states of the system in
order to make necessary adjustments when motor error occurs during movement. Previous studies on limb (Flanagan, Vetter, Johansson, & Wolpert, 2003; Wolpert, Ghahramani, & Flanagan, 2001) and speech motor control (Guenther, Ghosh, & Tourville, 2006; Hickok & Poeppel, 2004, 2007; Houde & Nagarajan, 2011) have suggested that these mechanisms follow the principles of the internal forward model theory.

An important proposal of the internal forward model theory is that temporal information processing is not merely mediated by an anticipatory mechanism in the sensory system (as suggested by the information processing theory), but this process involves predictive coding mechanisms in the motor system that can further enhance temporal information processing during movement. Supporting evidence for this notion has been provided by previous studies on hand movement (Bard et al., 1992; Blakemore, Wolpert, & Frith, 1998; Johansson & Westling, 1988; Witney, Goodbody, & Wolpert, 1999) and speech (Behroozmand, Liu, & Larson, 2011; Behroozmand, Sangtian, Korzyukov, & Larson, 2016; Chen, Chen, Liu, Huang, & Liu, 2012; Kotz & Schmidt-Kassow, 2015), demonstrating that when sensory stimuli arise from self-produced motor actions, the internal forward model predicts the temporal relationships between motor commands and their sensory consequences. Findings of these studies have indicated that temporally-predictable patterns can be learned by the internal forward model and subsequently modulate perceptual sensations arising from self-generated motor actions. During hand movement, the modulation of perceptual sensations has been shown to be reflected in attenuation of sensory responses to self-produced motor actions (Blakemore, Wolpert, & Frith, 2000; Blakemore et al., 1998) which is hypothesized to be caused by
central cancellation of sensory responses by the efference copies of the motor commands. In addition, studies have shown that the neural correlates of hand motor movement are differentially modulated by predictable vs. with unpredictable stimuli (Alegre et al., 2003; Bevan et al., 1965; Koppe et al., 2014; Schwartze, Rothermich, & Kotz, 2012), indicating that the internal predictive mechanisms are affected by temporal dynamics of environmental sensory cues. In the speech modality, studies have also demonstrated that neural responses to perturbations in speech auditory feedback are differentially suppressed in response to temporally-predictable vs. unpredictable sensory stimuli, with greater motor-induced suppression in response to predictable stimuli (Behroozmand et al., 2016).

Supporting evidence for the notion of motor system involvement in temporal information processing has been provided by neuroimaging studies, suggesting a functional disassociation between brain areas involved in processing temporally-predictable vs. unpredictable sensory stimuli (Thickbroom et al., 2000; Vallesi, McIntosh, Shallice, et al., 2009; Vallesi, Shallice, & Walsh, 2007). In one study (Thickbroom et al., 2000), it has been shown that the caudal segment of the supplementary motor area (SMA) exhibited a significant neural activity increase for movements initiated in response to temporally-unpredictable (irregular) vs. predictable (regular) sensory cues. Other studies have reported that areas within the right dorsolateral prefrontal cortex (rDLPFC) play a critical role in monitoring conditional probability of sensory stimuli while human subjects performed a motor response reaction time task during the FP paradigm (Vallesi, McIntosh, Shallice, et al., 2009; Vallesi et al., 2007). In addition, evidence from studies in Parkinson’s disease (PD) have suggested that
neurological damages to the basal ganglia and the corticostriatal network may disrupt temporal information processing, and subsequently decelerate motor responses to temporally-predictable, but not unpredictable sensory stimuli (Bloxham, Mindel, & Frith, 1984; Schwartze et al., 2012).

Although previous studies have provided insights into the mechanisms of temporal information processing during movement, our understanding of these mechanisms has been limited by a number of factors. First, previous studies have been mainly focused on investigating the effects of stimulus temporal predictability on motor reaction time only during initiation of hand movement. However, it is not clear whether initiation and inhibition of movement are driven by common or functionally distinct mechanisms in the brain. Studies have suggested that movement initiation is coordinated by motor planning and execution mechanisms within the primary and secondary cortical motor areas of the frontal lobe (e.g. inferior frontal gyrus, premotor and motor cortex, and SMA), whereas movement inhibition is controlled by the influence of subcortical neural circuits (e.g., basal ganglia) on cortical motor regions (Aron et al., 2007; Aron & Poldrack, 2006; Cai, Oldenkamp, & Aron, 2012; Markett et al., 2016). Although temporal predictions were shown to modulate reaction time for hand movement inhibition (Murray & Byrne, 2005), possible functional distinctions would imply differential effects of temporal predictability on motor reaction time during movement initiation and inhibition even though they may recruit common temporal predictive mechanisms. Second, it is still unclear to what extent speech production and hand movement share common mechanisms, and how temporal features of sensory stimuli are encoded by these two different motor control systems. Converging evidence has
suggested that the evolution of Broca’s area in the human brain may have provided a possible neural interface for cross-modality interaction between manual gestures and vocalization mechanisms for speech and language (Gentilucci, Campione, Dalla Volta, & Bernardis, 2009; Gentilucci & Volta, 2008). This notion was corroborated by studies demonstrating interactions between the speech and hand motor systems (Binkofski, Buccino, Posse, et al., 1999; Binkofski, Buccino, Stephan, et al., 1999; Corballis, 2003; Fadiga & Craighero, 2006; Gentilucci et al., 2009), suggesting that the mechanisms of speech and hand movement may share common neural mechanisms. However, the functional correlates of such possible interactions between the speech and hand motor systems remain to be elucidated.

The present study was motivated by the question whether temporal predictability of sensory cues would modulate movement reaction times during initiation and inhibition of speech and hand motor responses. We designed an experiment in which subjects performed a randomized speech (vowel vocalization) or hand (button press) motor response task in two counterbalanced blocks with temporally-predictable and unpredictable visual cues. The visual stimuli were presented to cue the subjects to first initiate and then inhibit the ongoing motor action during speech or hand movement tasks, with visual cues presented at either fixed or randomized time intervals during predictable and unpredictable blocks, respectively. We used the measure of motor response reaction time as a behavioral index of temporal information processing during speech production and hand movement. This novel experimental design provided a unified framework to simultaneously examine the effects of temporal predictability on the mechanisms of speech production and hand movement, and to compare the underlying mechanisms of
response initiation and inhibition in these two modalities. To our knowledge this is the first study that examined the effect of temporal predictability on the reaction time measures of movement initiation and inhibition in both speech and hand modalities. Based on the results of previous studies, we hypothesized to see faster reaction times in response to temporally-predictable compared with unpredictable sensory stimuli. However, we did not have enough empirical evidence to support the hypothesis that the measures of reaction time would differ across task (initiation vs. inhibition) and modality (speech vs. hand), regardless of the timing factor. Therefore, we took an exploratory approach and included timing, task, and modality in our analysis to examine whether the motor response reaction times would be modulated in response to predictable vs. unpredictable stimuli during initiation vs. inhibition of speech or hand movement. Findings of this study will provide new insights into the mechanisms of temporal information processing in the motor system driving speech production and hand movement.

2.3 Material and Methods

2.3.1 Subjects

15 healthy subjects (8 males and 7 females, age 20-30 years old) were recruited for this study. Subjects reported no history of psychiatry and neurological conditions and they had no history of speech or hearing impairment. All subjects also reported normal or corrected vision. Handedness of subjects was obtained using the Edinburg handedness inventory (Oldfield 1971), and it was determined that all subjects were right-handed (score range 72-100). All study procedures including recruitment, data acquisition and
informed consent were approved by the University of South Carolina Institutional Review Board, and subjects were monetarily compensated for their participation.

2.3.2 Experimental Design

The experiment consisted of two tasks that involved speech (steady vowel vocalization) and hand (button press) motor movements. Subjects were seated in a comfortable chair directly in front of the computer screen at a distance about 40-50 cm to easily see the presented visual cues. The background of the screen was black and the visual cues appeared as white circles at 1.5 inches in diameter. Because the speech motor task involved vowel sound vocalizations for which an auditory feedback signal was heard through earphones, visual stimuli were used to cue subjects to initiate and inhibit movements during each condition. If auditory cues were used, they could have been partially masked by the speech feedback signal, creating difficulties for the subjects to detect them accurately to start or stop vocalizations. Therefore, in order to avoid inconsistency, we used visual cues in both speech and hand movement tasks.

Subjects were asked to prepare to perform one of the above motor tasks (speech or hand) following the onset of a relevant visual cue on the screen (Figure 2.1). During the speech production task, subjects were presented with a picture illustrating human vocalization to prepare for speech movement, and were asked to start vocalizing a steady vowel sound /a/ after a black circle (go signal) appeared on the screen, and stop the vocalization after the circle disappeared (stop signal). During the hand movement task, subjects were presented with a picture illustrating button press to prepare for hand movement, and were asked to start pressing a button with the index finger of their
dominant hand (right in all subjects) after a black circle (go signal) appeared on the screen, and release it after it disappeared (stop signal). Subjects were given verbal instructions on how to perform the experimental tasks and they went through a short practice session (2-3 minutes) in order to ensure they knew how to perform the tasks correctly during each block. The experimenter approved that all subjects were able to perform the tasks correctly before data recording was started.

We designed two counterbalanced blocks within which subjects performed the speech and hand motor movement tasks in a randomized order: 1) temporally-predictable block, in which there was a fixed time interval of 1500 ms between the onset of the visual cue and go signal, as well as, between the go and stop signal, and 2) temporally-unpredictable block in which the time internal between visual cue and go signal, as well as, between go and stop signal was randomized between 1000-2000 ms. During each block, a total number of 220 trials were collected, with approximately 110 trials for speech and 110 trials for hand motor movement. The interval time between consecutive speech and hand movement trails was 2-3 seconds in both predictable and unpredictable blocks. Subjects took 5-minute breaks between two blocks. All the experimental parameters, including visual cues, go and stop signals and the time intervals between them was controlled by a custom-made program implemented in Max (Cycling '74, San Francisco, CA). Additionally, timing within trials (T1 and T2) and order of trials (speech and hand) were controlled by the Max program. Subjects’ responses including vowel sound vocalization and button press along with the onset of all visual cues were digitized at 44100 Hz and recorded on a laboratory computer for the analysis of the reaction time in each condition.
Figure 2.1 Experimental design for speech and hand motor reaction time tasks during (A) predictable and (B) unpredictable blocks. In each block, subjects were presented with a relevant face or hand picture on the screen (prepare signal) and were asked to vocalize the steady vowel /a/ (speech production) or press a button (hand movement) after a circle (go signal) appeared on the screen and stop the vocalization or release the button after the circle disappeared (stop signal). The background of the screen was black, and the visual cues appeared as white circles at 1.5 in. in diameter. In this figure, T1 (predictable interval) and T2 (unpredictable interval) indicate the time intervals between “prepare” and “go”, and the time interval between “go” and “stop” signals in either vocalization or button press task. For the predictable block, T1 was fixed at 1500 ms whereas for the unpredictable block, T2 was randomized between 1000–2000 ms. ITI represents the inter-trial-interval which was about 2–3 sec for both predictable and unpredictable conditions.

2.3.3 Reaction Time Analysis

For each subject, measures of reaction time were obtained for both predictable and unpredictable conditions during initiation and inhibition of speech and hand movement. A custom-made MATLAB code was used to load the subjects’ response files and extract the sample points (N) corresponding to the onset of all events including the visual cues (prepare, go, and stop) for each condition along with the initiation and inhibition of speech and hand movement responses. For hand movement, sample points were extracted at times when the subjects pressed/released the button. For speech...
movement, sample points were extracted at times when the subjects’ speech signal exceeded (initiation) or fell below (inhibition) a threshold at 10% of its peak amplitude. We further confirmed the results of this analysis by visually inspecting the output data files on a trial-by-trial basis to ensure that the samples of all events were extracted accurately. Measures of reaction time were calculated as the difference between the total number of sample points between the go/stop signals and subject’s’ speech or hand responses according to the following formula:

\[ RT = \frac{(N_{Response} - N_{Go/Stop})}{F_S} \times 1000 \]

In this formula, \(RT\) is the Reaction Time (in milliseconds), \(N_{Response}\) is the sample point corresponding to subject’s response (initiation or inhibition of speech or hand), \(N_{Go/Stop}\) is the sample point corresponding to the onset of Go or Stop visual cue, and \(F_S\) is the sampling frequency of the recorded data file (44100 Hz).

2.3.4 Statistical Analysis

A 2×2×2 repeated-measures analysis of variance (RANOVA) was performed to test the main effects of timing (predictable vs. unpredictable), modality (speech vs. hand) and task (initiation and inhibition), or their interactions on the measures of motor response reaction times. We have performed follow-up analyses to further explore the significant effects by separately examining the effects of timing, task and modality on the measures of reaction time. The initial alpha level was adjusted at \(p < 0.05\) and post-hoc tests were corrected for multiple comparisons using Bonferroni’s method.
2.3.5 Correlation Analysis

A Pearson’s correlation analysis with Bonferroni’s correction was performed to investigate the relationships between the reaction time measures within task (initiation vs. inhibition) and modality (speech vs. hand) factors separately for predictable and unpredictable conditions.

2.4 Results

The mean and standard deviation (SD) of the extracted reaction time measures are presented in table 2.1 during predictable and unpredictable conditions for modalities (speech vs. hand) and tasks (movement initiation vs. inhibition). Results of the statistical analysis yielded significant main effects of timing ($F_{(1,14)}=5.33, p<0.05$; longer latency for unpredictable), modality ($F_{(1,14)}=23.98, p<0.001$; shorter latency for hand) and task ($F_{(1,14)}=60.95, p<0.001$; longer latency for initiation). However, no interaction was found between timing, modality and task ($F_{(1,14)}=0.18, p>0.05$) factors or any 2×2 interactions between modality and timing ($F_{(1,14)}=0.867, p>0.05$), modality and task ($F_{(1,14)}=1.74, p>0.05$), and timing and task ($F_{(1,14)}=1.61, p>0.05$).

Table 2.1 The mean and standard deviation (SD) of reaction times during predictable and unpredictable conditions for speech and hand modalities and movement initiation and inhibition tasks.

<table>
<thead>
<tr>
<th></th>
<th>Speech</th>
<th>Button press</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initiation</td>
<td>Inhibition</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Predictable</td>
<td>442</td>
<td>27</td>
</tr>
<tr>
<td>Unpredictable</td>
<td>461</td>
<td>19</td>
</tr>
</tbody>
</table>
2.4.1 The Effect of Temporal Predictability

Timing effect analysis revealed that movement inhibition was faster during predictable compared with unpredictable conditions for both speech ($t_{(14)}= 2.23, p<0.05$) and hand ($t_{(14)}= 2.89, p<0.05$) modalities (Figure 2.2). However, there was no significant difference between predictable and unpredictable initiation for hand and speech ($p >0.05$), even though response time was faster for movement initiation during the predictable condition. Figure 2.2 illustrates an example of bar plot representation for the differences between reaction time measures in response to predictable and unpredictable conditions during initiation and inhibition of speech (A) and hand (B) movement.

2.4.2 Hand vs. Speech Modality

Across-modality analysis indicated that during the predictable condition, the reaction time of the hand responses were significantly shorter (faster movement) compared with speech during both initiation ($t_{(14)}= 5.86, p<0.001$) and inhibition ($t_{(14)}= 2.42, p<0.05$) tasks. In addition, for the unpredictable condition, a longer response latency was found for speech during both initiation ($t_{(14)}= 4.85, p<0.001$) and inhibition ($t_{(14)}= 2.49, p<0.05$) tasks.

2.4.3 Movement Initiation vs. Inhibition

Within-modality comparisons indicated that reaction time was significantly longer for movement initiation in both predictable ($t_{(14)}= 5.05, p<0.001$) and unpredictable ($t_{(14)}= 5.46, p<0.001$) conditions during speech production. Similarly, during hand
movement, reaction times were significantly longer for movement initiation during both predictable ($t_{(14)}=5.77$, $p<0.001$) and unpredictable ($t_{(14)}=5.08$, $p<0.001$) conditions.

Figure 2.2 Comparison between movement reaction times during predictable vs. unpredictable conditions. Panel A shows the responses to predictable and unpredictable stimuli during speech production. Panel B displays the responses to predictable and unpredictable stimuli during hand movement.

2.4.4 Correlation Analysis

Results of the correlation analysis revealed that the reaction time during hand initiation was correlated with speech movement initiation ($r=0.93$, $p<0.001$; corrected) (Figure 2.3.A). In addition, the reaction time during hand movement inhibition was correlated with hand movement initiation ($r=0.82$, $p<0.001$; corrected) (Figure 2.3.B). Lastly, we found a significant positive correlation between reaction times during speech initiation and speech inhibition ($r=0.82$, $p<0.001$; corrected) (Figure 2.3C). During the unpredictable conditions, the measures of reaction time for hand initiation were positively correlated with hand inhibition ($r=0.71$, $p<0.05$; corrected) and speech initiation ($r=0.72$, $P<0.05$; corrected) (Figures 2.4 A and B).
Figure 2.3 Results of the correlation analysis for hand and speech movement initiation and inhibition reaction times (in milliseconds) during the predictable condition. Panel A shows the relationship between speech and hand movement initiation. Panel B displays the relationship between hand movement initiation and inhibition. Panel C shows the relationship between speech initiation and inhibition reaction times.

Figure 2.4 Results of the correlation analysis for hand and speech movement initiation and inhibition reaction times (in milliseconds) during the unpredictable condition. Panels A show hand initiation reaction time vs. hand inhibition. Panel B displays the relationship between reaction time of speech initiation and hand initiation.
2.5 Discussion

In the present study, we investigated the effect of temporal predictability on motor reaction time during initiation and inhibition of speech and hand movement. The major hypothesis was that motor responses would be executed faster (shorter reaction time) when the externally-presented visual stimuli were temporally-predictable. We also predicted to observe the effect of stimulus temporal predictability on response reaction times in both hand and speech modalities, as well as movement initiation and inhibition tasks. These hypotheses were tested by measuring reaction time of hand and speech responses in response to visual cues presented with temporally-predictable and unpredictable patterns. In what follows, we have discussed our findings in the context of earlier information processing and more recent internal forward model theories of movement and incorporated them with results from previous studies to provide insights into the mechanisms of temporal information processing during movement.

2.5.1 Temporal Predictability Effect

Results of our analysis confirmed our hypothesis about the modulation of motor reaction times in response to temporally-predictable compared with unpredictable stimuli. We found that, regardless of movement modality, temporally-predictable stimuli elicited faster motor responses (shorted reaction time) compared with unpredictable stimuli. This finding is consistent with previous studies showing that stimulus predictability can elicit motor responses with shorter reaction times during initiation and inhibition phases of movement (Koppe et al., 2014; Kotz & Schmidt-Kassow, 2015; Niemi & Naatanen, 1981; Vallesi, McIntosh, Shallice, et al., 2009). However, we found that the stimulus predictability did not induce equal effects on modulation of reaction time measures.
during movement initiation and inhibition tasks. Within-modality analysis showed that the timing difference was more pronounced during inhibition of movements than initiation.

Faster motor responses to temporally-predictable stimuli are largely supported by the information processing account, suggesting that a higher level of readiness during fixed-interval (predictable) stimuli enhances the temporal estimation of upcoming imperative signals, whereas variable intervals can increase temporal uncertainty and lead to longer reaction times (Bertelson & Boons, 1960; Bevan et al., 1965; Klemmer, 1956). In the present study, we showed that temporally-predictable stimuli provided a higher level of readiness for upcoming visual cues (go and stop), while unpredictable cues led to an increase in temporal uncertainty and a subsequent slowing of movement initiation and inhibition in both speech and hand modalities. Although the information processing model (Karlin, 1959) has proposed that this effect is accounted for by a temporal predictive code established in the sensory system, more recent models of sensorimotor integration have argued that the internal forward model of the motor system may contribute to such a predictive code to facilitate temporal information processing during movement (Witney et al., 1999; Wolpert, 1997; Wolpert et al., 2011; Wolpert & Flanagan, 2001; Wolpert et al., 2001).

Findings of previous studies have indicated that temporal relationships between motor commands and their sensory consequences can be predicted by the internal feedforward mechanisms of the motor system (Miall & Wolpert, 1996; Wolpert & Flanagan, 2001). Evidence from studies in hand (Blakemore et al., 2000; Blakemore et al., 1998) and speech (Behroozmand et al., 2016) modalities corroborated this notion by
showing that the motor-induced suppression of sensory neural responses to self-produced movements are greater for temporally-predictable compared with unpredictable stimuli. Results of these studies have suggested that a temporal predictive code is established by the internal forward model of the motor system to cancel out sensory consequences of self-produced motor actions with high temporal acuity. These findings provide supporting evidence for the involvement of the internal forward motor mechanisms in establishing a temporal predictive code during speech and hand movement.

Further support for the notion of motor system involvement in temporal information processing has been provided by previous studies showing that cortical motor areas within the caudal segment of SMA (Thickbroom et al., 2000; Vallesi, McIntosh, Shallice, et al., 2009) and rDLPFC (Vallesi, McIntosh, Shallice, et al., 2009; Vallesi et al., 2007) exhibit stronger neural activities in response to temporally-unpredictable compared with predictable sensory stimuli. Previous studies have also identified specific neural response components that serve as neurophysiological correlates of temporal information processing in the brain (Alegre et al., 2003; Schmitz, Jenmalm, Ehrsson, & Forssberg, 2005; Thickbroom et al., 2000; Vallesi, McIntosh, Shallice, et al., 2009). An event-related desynchronization (ERD) of beta band activity (13-30 Hz) has been shown to be elicited only in response to temporally-predictable stimuli during movement (Alegre et al., 2003), suggesting that this ERD component is a neurophysiological correlate of temporal information processing during hand movement. More importantly, the beta-ERD activity for predictable stimuli has been shown to be a pre-movement component, suggesting that it may reflect a predictive code that is established in the feedforward motor mechanisms during the preparatory phase of
movement in response to temporally-predictable sensory patterns. We propose that this predictive code may be involved in estimating the temporal aspects of upcoming sensory events that are predictable in nature to prepare and optimize motor commands for faster movements. Moreover, other studies have also reported that desynchronization of beta band activity within the subthalamic nucleus (STN) of basal ganglia prior to the onset of externally-induced or self-paced movements might be an indication of predictive strategies used for preparation of movement (Kühn et al., 2004). It can be suggested that the decreased reaction time in response to temporally-predictable cues in the present study may be driven by similar beta-band pre-motor activities in both speech and hand modalities in response to sensory stimuli with temporal regularity.

In this context, we propose that modulation of motor reaction times in response to temporally-predictable vs. unpredictable stimuli is indicative of an established temporal predictive code during initiation and inhibition of movement in both speech and hand modalities. According to the temporal information processing model (Karlin, 1959), our findings suggest that this predictive code receives contribution from the sensory mechanisms involved in extracting timing information from stimuli that follow a temporally-regular pattern. Although our experimental paradigm does not provide a framework to determine the contribution of the motor system, evidence from previous studies has suggested that the internal forward mechanisms may also contribute to the temporal predictive code in order to finetune motor commands for performing movements with finer temporal precisions (Witney et al., 1999; Wolpert, 1997; Wolpert et al., 2011; Wolpert & Flanagan, 2001; Wolpert et al., 2001). As suggested by those studies, the feedforward motor system is involved in establishing internal predictions to
capture temporal dynamics of the external sensory cues, and subsequently drive
movement responses with significantly shorter reaction times. We propose that a similar
mechanism may have been involved in extracting temporal regularities in the pattern of
external visual stimuli in the present study to drive faster motor movements in response
to temporally-predictable sensory stimuli. However, further examinations in future
studies will be required to validate these proposals and to determine the degree of such
possible contributions from the motor system for establishing a temporal predictive code
during speech and hand movement.

The decreased reaction time (faster responses) for predictable stimulus-induced
movement in our study can also be discussed in relation to the neural activation threshold
theory. According to this theory, movement is initiated when the summative neural
activities in the motor cortex reach a specific threshold level (Hanes & Schall, 1996). In
our study, the only different aspect of visually-presented stimuli was the pattern of their
temporal predictability, wherein predictable stimuli were presented with a fixed ISI and
unpredictable stimuli were presented with irregular and variable temporal patterns
(randomized ISI). We suggest that the shorter movement response time for predictable
stimuli in our study may reflect a mechanism that reduces the time window for reaching
the neural activation threshold in the motor cortical areas for generating faster movement
responses. It is likely that such a mechanism may use temporal regularity to efficiently
integrate and synchronize neural activities across multiple sensorimotor brain areas to
facilitate rapid movements in response to predictable sensory events. It is also possible
that temporal dynamics in predictable stimuli may further enhance movement processes
by providing a priming signal for the motor system to produce faster responses. However,
since unpredictable stimuli do not follow a temporally-regular pattern, reaching the motor activation threshold will take a longer time which subsequently leads to slower movements in response to visually-presented sensory cues.

2.5.2 Modality Effect

In previous studies, the mechanisms of motor control have been investigated independently for speech production (Behroozmand et al., 2011; Behroozmand et al., 2016; Guenther, 2006; Guenther et al., 2006; Hickok, Houde, & Rong, 2011) and hand movement (Alegre et al., 2003; Koppe et al., 2014; Kotz & Schmidt-Kassow, 2015; Wolpert et al., 2011; Wolpert et al., 2001). To our knowledge, the present study is the first to simultaneously investigate the effects of stimulus temporal predictability on speech and hand motor reaction time using a unified and consistent experimental paradigm. Our findings revealed that, regardless of stimulus temporal predictability, initiation and inhibition of hand movement were executed with shorter reaction times compared with speech. We suggest that this effect is accounted for by the inherent complexity of the speech motor task involving a temporally-coordinated sequential activation of a large group of muscles (e.g. respiratory, laryngeal, articulatory, tongue and facial muscles) compared with button press. Consistent findings in previous studies support this idea by showing that complex movements require a longer processing time to be executed (Gajewski & Falkenstein, 2013; Ma & Trombly, 2004).

Despite the fact that hand movement was executed faster than speech, a significant decrease in speech and hand motor reaction times in response to predictable stimuli suggest that the feedforward mechanisms of speech and hand may share common
neural mechanisms while they serve distinct functions in the human brain. Previous studies have supported this notion by demonstrating interactions between the speech and hand motor systems (Binkofski, Buccino, Posse, et al., 1999; Binkofski, Buccino, Stephan, et al., 1999; Corballis, 2003; Fadiga & Craighero, 2006; Gentilucci et al., 2009). It has been argued that such cross-modality interaction may have arisen because of an evolutionary association between manual gestures and vocalization mechanisms for speech and language; a transition that may be traced through functional development of Broca’s area in the human brain (Gentilucci et al., 2009; Gentilucci & Volta, 2008). Neuroimaging studies have demonstrated that Broca’s area is activated during meaningful gestures (Gentilucci et al., 2009; Gentilucci & Volta, 2008), manual grasping (Binkofski, Buccino, Posse, et al., 1999; Gerardin et al., 2000; Grezes, Armony, Rowe, & Passingham, 2003) and speech production (Papathanassiou et al., 2000), suggesting that this area may serve as a neural interface for speech and hand motor interactions. In addition, one recent study has shown that inhibition of speech movement engages a mechanism that has global suppressive effects on the motor system including the hand movement modality (Cai et al., 2012). These findings suggest that the observed modality-specific effect in the present study may be attributed to inherent differences in the degree of complexity for speech and hand movement, but similar effects of stimulus timing on these modalities is an indication that temporal information processing may be mediated by common predictive coding mechanisms during speech and hand movement.

2.5.3 Task Effect

We found that response time was significantly longer for movement initiation in both predictable and unpredictable conditions regardless of modality. This effect can be
explained by the fact that, in general, movement initiation is driven by a more complex mechanism that involves a motor program for sequential activation of a group of muscles with a specific timing pattern in order to reach the goals of the tasks during speech (producing the vowel sound) and hand movement (pressing a button). However, movement inhibition in our experimental task (stopping the vowel production or releasing the button) may have required a less complex mechanism because it does not involve a motor program for deactivating muscles to stop the ongoing motor action. Therefore, the observed effect associated with longer reaction times for movement initiation may be explained by the difference in complexity level of the mechanisms that drive movement initiation compared with inhibition. It is also noteworthy to mention that in our experiment, subjects were aware that they should be ready to start or stop movements in response to the onset of a specific cue; therefore initiation and inhibition of movement shared the preparatory mechanisms that were required for activating (initiation) or deactivating (inhibition) muscle movements during the tasks. Based on this effect, we suggest that the difference in reaction time between movement initiation and inhibition may be accounted for by the difference in programming and execution of motor commands, but not the planning of movements.

2.5.4 Behavioral Correlation

Results of our correlation analysis indicated that the reaction time of movement initiation and inhibition in both hand and speech modalities were positively correlated. This finding implies that a person with faster reaction times for movement initiation will be more likely to exhibit faster reaction times for movement inhibition, and vice versa.
This finding is consistent with results from a previous study showing that readiness prior to movement onset can modulate reaction time of movement inhibition (Murray & Byrne, 2005). Therefore, it can be suggested that temporal readiness for movement initiation might also reduce movement inhibition reaction time. Additionally, the correlation results indicate that temporal information processing may share common neural mechanisms for both movement initiation and inhibition tasks. Moreover, we found a positive correlation between hand and speech initiation reaction times, suggesting that faster movements in speech modality may generalize to other non-speech modalities (e.g., hand movement), and vice versa. The correlation between speech and hand motor reaction times provide further support for an interactive cross-modality model of speech and hand movement as proposed by previous studies (Binkofski, Buccino, Posse, et al., 1999; Binkofski, Buccino, Stephan, et al., 1999; Cai et al., 2012; Corballis, 2003; Gentilucci et al., 2009; Gentilucci & Volta, 2008). These findings provide new insights into the processes that underlie movement production and suggest that in general the brain may fundamentally share a common neural mechanism for processing temporal dynamics of sensory stimuli to drive movement initiation and inhibition in both hand and speech modalities.

2.6 Conclusion

The present study entailed a systematic investigation on the effects of stimulus temporal predictability on motor reaction times of speech and hand movement. Our results provided evidence that the functional behavior of the motor system, as indexed by reaction time, is modulated by temporal dynamics of sensory cues in a task- and modality-specific manner. We showed that temporal predictability facilitated motor
reaction time during speech and hand movement, and inhibitory responses were faster than movement initiation. In addition, hand motor responses were found to be generally faster than speech. These findings support the notion that a temporal predictive code is established to facilitate movement in response to externally-presented sensory cues. We propose that this predictive code receives contribution from sensory mechanisms of temporal information processing, and may be further enhanced by the internal forward mechanisms of speech and hand movement. However, important questions remain as to how such a temporal predictive code is established in the brain, and how this information is used to fine tune motor commands for driving behaviorally-relevant movements with a high degree of temporal precision.
Chapter 3

---

3.1 Abstract

The predictive coding model suggests that neural processing of sensory information is facilitated for temporally-predictable stimuli. This study investigated how temporal processing of visually-presented sensory cues modulates movement reaction time and neural activities in speech and hand motor systems. Event-related potentials (ERPs) were recorded in 13 subjects while they were visually-cued to prepare to produce a steady vocalization of a vowel sound or press a button in a randomized order, and to initiate the cued movement following the onset of a go signal on the screen. The experiment was conducted in two counterbalanced blocks in which the time interval between visual cue and go signal was temporally-predictable (fixed delay at 1000 ms) or unpredictable (variable between 1000-2000 ms). Results of the behavioral response analysis indicated that movement reaction time was significantly decreased for temporally-predictable stimuli in both speech and hand modalities. We identified premotor ERP activities with a left-lateralized parietal distribution for hand and a frontocentral distribution for speech that were significantly suppressed in response to temporally-predictable compared with unpredictable stimuli. The premotor ERPs were elicited approximately -100 ms before movement and were significantly correlated with speech and hand motor reaction times only in response to temporally-predictable stimuli. These findings suggest that the motor system establishes a predictive code to facilitate movement in response to temporally-predictable sensory stimuli. Our data suggest that the premotor ERP activities are robust neurophysiological biomarkers of such predictive coding mechanisms. These findings provide novel insights into the temporal processing mechanisms of speech and hand motor systems.
3.2 Introduction

Movement production is a fundamentally important function of the central nervous system that enables humans and animals to interact with their environment through generating motor behavior in response to sensory stimuli. A critical aspect of movement is to incorporate sensory information and execute motor responses with high temporal precision in order to accomplish the goals of a behaviorally-relevant task (e.g., driving a car, walking, hitting a tennis ball or speaking to a friend). However, the underlying mechanisms of temporal processing during movement remain poorly understood. In addition, studies in patients with neurological disorders such as those with Parkinson’s disease (PD) have demonstrated that dysfunction in basal ganglia and other movement-related brain areas may interrupt the temporal processing mechanisms involved in programming and synchronization of motor responses, which can subsequently lead to decelerated (slower) motor reaction times for movement initiation (Bloxham et al., 1984; Bloxham, Dick, & Moore, 1987; Ivry & Keele, 1989; Jahanshahi, Jones, Dirnberger, & Frith, 2006; Pastor, Artieda, Jahanshahi, & Obeso, 1992).

Therefore, gaining knowledge about the association between temporal processing and motor behavior will have important clinical implications to improve diagnosis and maximize treatment outcome in neurological patients with movement disorders. The present study is a key step toward this goal and performs a systematic investigation on the dynamics of the mechanisms that mediate hand and speech movement in response to temporally-predictable and unpredictable sensory stimuli in healthy individuals.

The sensory mechanisms of temporal information processing have previously been studied using the classical odd-ball paradigm in which a mismatch negativity
(MMN) component is elicited in the brain in response to a deviant sensory stimulus that violates an established pattern (Näätänen, Paavilainen, Rinne, & Alho, 2007; Symonds et al., 2016; Wacongne, Changeux, & Dehaene, 2012). Previous studies have suggested that the brain extracts temporal information by showing that an MMN component is elicited in response to auditory stimuli that violated patterns established in response to sounds presented with temporally-predictable duration or intervals (Cornella, Leung, Grimm, & Escera, 2012; Moberget et al., 2008; Schwartze, Rothermich, Schmidt-Kassow, & Kotz, 2011; Toyomaki et al., 2008; van Zuijen, Sussman, Winkler, Näätänen, & Tervaniemi, 2005). In addition, the mechanisms of temporal information processing during movement have been investigated by other studies using the foreperiod (FP) paradigm in which the time interval between a warning and an imperative signal is manipulated while subjects perform a motor response reaction time task (Drazin, 1961; Karlin, 1959; Klemmer, 1956). Results of these studies have indicated that for variable FPs, the motor response reaction time was increased and negatively accelerated as a function of the FP duration. In addition, temporally-predictable FPs with fixed durations were shown to elicit movements with shorter reaction times compared with variable FPs, suggesting that the pattern of temporal regularity in FP can modulate reaction time for motor responses during movement initiation (Bertelson & Boons, 1960). A consistent effect has also been reported by other studies in which the inter-stimulus interval (ISI) was manipulated during motor response reaction time tasks (Bevan et al., 1965; Mattes & Ulrich, 1997; Niemi & Naatanen, 1981; Timm, Schonwiesner, Schroger, & SanMiguel, 2016; Vallesi, McIntosh, Shallice, et al., 2009). Findings of these studies revealed that the reaction time for initiating hand motor responses was significantly shorter and movements were
performed with a greater temporal precision in response to fixed ISI (predictable) compared with variable (unpredictable) sensory stimuli. In this context, an important question remains as to how temporal information is processed to drive faster movements in response to temporally-predictable sensory stimuli.

Recent models of movement production have suggested that the brain can internally simulate the behavior of the motor system during planning, execution and control of movement (Mendoza & Merchant, 2014; Miall & Wolpert, 1996; Wolpert, 1997). It has been hypothesized that these internal simulations facilitate movement through using the intrinsic features of motor commands to predict the sensory consequences of self-generated movements. This hypothesis has been expounded by the internal forward model theory (Wolpert et al., 2011; Wolpert & Flanagan, 2001) in which a forward model learns the relationship between the efference copies of the motor commands and their sensory feedback in order to fine tune motor commands and control them during movement. The consequence of this process is the generation of a predictive code that estimates the current and future states of the motor system and makes adjustments when errors occur during movement. The recent models of limb (Flanagan et al., 2003; Wolpert et al., 2001) and speech (Guenther et al., 2006; Hickok & Poeppel, 2004, 2007; Houde & Nagarajan, 2011) motor control have proposed that these processes follow the principles of the internal forward model theory.

More recent studies have suggested that when sensory stimuli arise from self-produced motor actions, the internal forward model can establish predictions about the temporal relationships between the motor commands and their sensory feedback during hand movement (Bard et al., 1992; Blakemore et al., 1998; Johansson & Westling, 1988;
Witney et al., 1999) and speech production (Behroozmand et al., 2011; Behroozmand et al., 2016; Chen et al., 2012; Kotz & Schmidt-Kassow, 2015). These studies have suggested that temporally-predictable patterns in sensory consequences of self-generated motor actions can be learned by the internal forward model. In addition, neural responses to sensory feedback from self-produced hand (Blakemore et al., 2000; Blakemore et al., 1998) and speech (Behroozmand & Larson, 2011; Behroozmand et al., 2016; Chang, Niziolek, Knight, Nagarajan, & Houde, 2013; Houde, Nagarajan, Sekihara, & Merzenich, 2002) movements were shown to be suppressed, and this motor-induced suppression was hypothesized to be resulting from cancellation of neural activities by the efference copies of the motor commands. In the speech modality, the motor-induced suppression effect has been shown to be stronger in response to temporally-predictable vs. unpredictable perturbations in the auditory feedback, suggesting that the contribution of the feedforward motor mechanisms is increased for regulating speech motor commands in response to predictable stimuli (Behroozmand et al., 2016).

Novel insights into the mechanisms of temporal processing during movement have been provided by neuroimaging studies that indicated functional disassociation between brain regions involved in processing sensory stimuli with predictable vs. unpredictable temporal patterns (Thickbroom et al., 2000; Vallesi, McIntosh, Shallice, et al., 2009; Vallesi et al., 2007). These studies have shown that neural activities in the caudal portion of the supplementary motor area (SMA) (Thickbroom et al., 2000), as well as the right dorsolateral prefrontal cortex (DLFPC) (Vallesi, McIntosh, Shallice, et al., 2009; Vallesi et al., 2007) were significantly stronger when movements were initiated in response to temporally-unpredictable compared with predictable stimuli. In contrast,
neural activities in the left inferior parietal cortex (IPC) were reported to be preferentially stronger for movements in response to temporally-predictable vs. unpredictable stimuli (Coull, Cotti, & Vidal, 2016). In addition, single unit recordings from medial premotor cortex (MPC) in monkeys have shown that neurons in this area not only encode temporally-predictable intervals in sensory stimuli but are also activated to generate timed intervals during rhythmic movements (Crowe, Zarco, Bartolo, & Merchant, 2014; Merchant et al., 2015; Merchant, Pérez, Zarco, & Gámez, 2013). This suggests that neurons in the premotor cortex are part of a timing network that uses interval tuning to process temporal regularity during a variety of behaviorally-relevant motor tasks. These findings provide supporting evidence for the existence of specialized neural networks that differentially process timing information during movement in response to temporally-predictable and unpredictable sensory stimuli.

Although stimulus temporal predictability was shown to modulate neural activities after the onset of movement, a number of other studies have reported that pre-movement neural activities are also modulated in responses to temporally-predictable vs. unpredictable sensory stimuli (Alegre et al., 2003; Baker, Piriapunyaporn, & Cunnington, 2012; Kühn et al., 2004). Electroencephalography (EEG) recordings in humans have demonstrated that pre-movement neural activities are elicited up to two seconds before the onset of the motor action, and were found to be stronger in scalp electrodes over the bilateral frontal areas (Baker et al., 2012). In addition, event-related desynchronization (ERD) of beta band (13-30 Hz) activities was reported in contralateral central electrodes prior to the onset of hand motor responses to temporally-predictable sensory stimuli (Alegre et al., 2003). Moreover, beta band desynchronization in
subthalamic nucleus (STN) of basal ganglia was also observed prior to the onset of self-paced movements or movement produced in response to temporally-predictable external stimuli, suggesting that STN may provide the neural substrate for a temporal predictive mechanism used for movement planning and execution (Kühn et al., 2004). PD patients manifest slower attenuation of preparatory beta band ERD activity, which reflects their deficit in processing temporal information for motor planning and execution (Praamstra & Pope, 2007). This effect has been suggested to result from neural deficits in basal ganglia within the corticostriatal network that are involved in processing timing information prior to movement onset.

In the present study, we recorded EEG signals to address the question how temporal aspects of sensory stimuli are processed and used by the brain to fine tune motor responses during hand movement and speech production. We designed an experiment in which human subjects were cued (in a randomized order) to prepare to press a button or vocalize a vowel sound following the onset of a task-relevant hand or speech visual cue, respectively. The experiment consisted of two counterbalanced blocks (predictable and unpredictable) in which the timing interval between the warning (prepare) and imperative signal (go) was either predictable (fixed) or unpredictable (variable). This novel experimental design allowed us to examine the effects of temporal predictability on neural mechanisms of hand and speech movement simultaneously. We hypothesized that a premotor neural activity would reflect mechanisms of motor planning and preparation for both hand and speech modalities, and this neural response would be modulated by the temporal aspects of visual cue stimuli. We also hypothesized that temporally-predictable stimuli would elicit faster motor responses, and movement
reaction times would be accounted for by the premotor neural activities in both hand and speech modalities.

3.3 Materials and Methods

3.3.1 Subjects

13 healthy subjects (7 females, age 20-30 years old) were included in this study. Subjects in this study were the same subjects who underwent behavioral testing in the study presented in chapter 2, except that we excluded two subjects because their EEG signals were largely contaminated by noise and muscle artifact and could not be used for the purpose of data analysis. Subjects reported no history of psychiatry, neurological and speech disorder. All subjects had normal vision and hearing. Handedness of subjects obtained using Edinburg handedness inventory (Oldfield 1971), and they were all right handed (score range 72-100). All study procedures, including recruitment, data acquisition and informed consent were approved by the University of South Carolina Institutional Review Board, and subjects were monetarily compensated for their participation.

3.3.2 Experimental Design

The experiment was conducted in a sound attenuated booth in which subjects performed the experimental tasks while the EEG signals were recorded. The experiment consisted of two random-order tasks that involved speech and hand movements. Subjects were instructed to prepare to perform one of the above motor tasks (speech or hand) following the onset of a relevant visual cue on the screen (see Figure 3.1 for experimental design). During each task, subjects were instructed to prepare for the cued movement and start pressing a button or vocalizing a steady vowel sound /a/ after a black circle (go
signal) appeared on the screen and stop after the circle disappeared. We designed two counterbalanced blocks within which subjects performed the speech and hand movement tasks in a randomized order: 1) temporally-predictable block, in which there was a fixed time interval (T1) of 1500 ms between the onset of the task-relevant visual cue and go signal and 2) temporally-unpredictable block in which the time internal between task-relevant visual cue and go signal (T2) was randomized between 1000-2000 ms. During each block, a total number of 220 trials were collected, with approximately 110 trials for speech and 110 trials for hand movement. The inter-trial-interval (ITI) was 2-3 seconds in each block and subjects took 5 minutes break between two blocks. All the experimental parameters, including visual cues, go signals and the time intervals were controlled by a custom-made program implemented in Max 5.0 (Cycling ‘74, San Francisco, CA). Additionally, timing within trials (T1 and T2) and the order of trials (speech and hand) were controlled by the Max program. Subjects’ responses including vowel sound vocalizations and button presses were digitized at 44100 Hz and recorded on a laboratory computer for the analysis of the reaction time and time-locked averaging of the ERPs to motor responses in each experimental condition.

3.3.3 Behavioral and EEG Data Acquisition

Speech motor responses to the “go” signal were registered by recording the subject’s voice using a head-mounted AKG condenser microphone (model C520) connected to a Motu Ultralite-MK3 amplifier. Hand motor responses to the “go” signal were registered by recording the subject’s button press on the space key of a standard Dell PC keyboard. Voice and button press responses were recorded at 44.1 kHz on a laboratory computer utilizing Max 5.0 (Cycling’ 74).
Figure 3.1 Experimental design of the motor reaction time task for A) temporally predictable and B) unpredictable blocks. In each block, subjects were presented with a task-relevant visual cue (limb or speech) and were instructed to prepare to press a button or vocalize the vowel /a/ after a circle (go signal) appeared on the screen and stop after it disappeared. In this figure, T indicates the time interval between “Preparation” and “Go” in either button press or vocalization task. For the predictable block, the time interval (T1) was fixed at 1500 ms, whereas for the unpredictable block, the time interval (T2) was randomized between 1000-2000 ms. ITI represents the inter-trial-interval which was about 2-3 seconds for both predictable and unpredictable conditions.

The Max 5.0 program controlled all aspects of the task-relevant visual cues and go signals and generated TTL pulses to mark the onset of each event during movement preparation and initiation across all trials in both temporally-predictable and unpredictable stimulus blocks. The EEG signals were recorded from 64 sites on the subject’s scalp using the Brain Vision active electrode system (Brain Products GmbH, Germany) placed on a standard electrode cap (Easy-Cap GmbH, Germany). The electrode placement on the cap followed the standard 10-20 montage and the EEG signals were recorded using a common reference. A BrainVision actiCHamp amplifier (Brain Products GmbH, Germany) on a computer utilizing Pycorder software recorded the EEG signals.
signals at 1 kHz sampling rate after applying a low-pass anti-aliasing filter with 200 Hz cut-off frequency.

3.3.4 Reaction Time Analysis

Motor reaction time for hand movement was calculated on a trial-by-trial basis as the time difference between the onset of the go signal and the onset of the subjects’ button press in predictable and unpredictable blocks, separately. Motor reaction time for speech movement was calculated on a trial-by-trial basis as the time difference between the onset of the go signal and the subject’s voice onset during vowel sound production in predictable and unpredictable blocks.

3.3.5 ERP Analysis

The EEGLAB toolbox (Delorme & Makeig, 2004) was used to analyze recorded EEG signals in order to extract ERPs time-locked to the onset of hand and speech movement during predictable and unpredictable conditions. The recorded EEGs were first filtered offline using a band-pass filter with cut-off frequencies set to 1 and 30 Hz (−24 dB/oct) and then segmented into epochs ranging from −200 ms before and 500 ms after the onset of the hand and speech movement. Following segmentation, artifact rejection was carried out to remove muscle and eye-blink activities by excluding epochs with EEG amplitudes exceeding ±50 μV. Individual epochs were then subjected to baseline correction by removing the mean amplitude of the pre-stimulus time window from −200 to -100 ms for each electrode. The extracted epochs were then averaged across all trials separately for each condition to obtain ERP responses for hand and speech.
movement onset. A minimum number of 80 trials for each condition were used to calculate ERP responses for each individual subject. The extracted ERP profiles were then averaged across all subjects to calculate the grand-average ERP responses.

3.3.6 Statistical Analysis and Power

Repeated-measures analysis of variance (Rm-ANOVA) implemented in SPSS 23.0 (IBM Inc.) was used to investigate the main effects of timing (predictable vs. unpredictable) and modality (speech vs. hand), and their interactions on behavioral measures of motor reaction time and neurophysiological ERP responses to hand and speech movement onset. Post-hoc analysis using Bonferroni’s correction for multiple comparisons was carried out to further examine interactions between timing and modality effects for each measure. Partial Eta-squared ($\eta^2_p$) values were reported as an index of effect size for significant main effects and interactions (Lakens 2013). We observed that for all significant results, data led to large effect sizes (all $\eta^2_p > 0.3$; see below). Power analysis was performed in G*Power toolbox (Erdfelder, Faul, & Buchner, 1996; Faul & Erdfelder, 1992) to obtain the power of each test based on the reported $\eta^2_p$ values. Results showed that the statistical power ($\beta$) was greater than 0.8 for all significant main effects and interactions, suggesting an adequate sample size in the present study.

3.4 Results

3.4.1 Reaction time results

A 2×2 Rm-ANOVA was used to investigate main effects of timing (predictable vs. unpredictable) and modality (speech vs. hand), and their interactions on motor
reaction times. Results revealed a significant main effect of timing ($F_{(1,12)}=4.7, p<0.05$, $\eta^2_{p}=0.33$), indicating faster motor reaction times (shorter latencies) for predictable compared with unpredictable condition. Results also revealed a significant main effect of modality ($F_{(1,12)}=34.12, p<0.001$, $\eta^2_{p}=0.76$), indicating faster motor reaction times for button press (hand) compared with the vowel vocalization (speech) task. However, there was no significant interaction between timing and modality ($F_{(1,12)}=0.001, p>0.05$, $\eta^2_{p}=0.0001$). The means and standard deviations of motor reaction times are reported for timing and modality factors in table 3.1.

Table 3.1 Mean and standard deviation of speech and hand motor reaction time (in milliseconds) for predictable and unpredictable conditions.

<table>
<thead>
<tr>
<th></th>
<th>Predictable</th>
<th>Unpredictable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Speech</td>
<td>433.12 (109.40)</td>
<td>466.13 (78.62)</td>
<td>449.63 (74.27)</td>
</tr>
<tr>
<td>Hand</td>
<td>371.23 (84.97)</td>
<td>407.70 (59.92)</td>
<td>388.96 (94.84)</td>
</tr>
<tr>
<td>Total</td>
<td>402.18 (101.03)</td>
<td>436.41 (74.89)</td>
<td>-------- (------)</td>
</tr>
</tbody>
</table>

3.4.2 ERP Results

The visual inspection of ERP profiles in all electrodes and their scalp topographical distribution maps revealed that the most prominent neural activities were elicited in response to hand and speech movement onset in electrodes near the midline with locations spanning anteriorly from frontal to posteriorly toward parietal areas. Therefore, we selected ERP data in 12 electrodes near the midline symmetrically-distributed over the left and right frontal (F1 and F2), frontocentral (FC1 and FC2),
central (C1 and C2), centroparietal (CP1 and CP2), medial parietal (P3, P4) and lateral parietal (P5 and P6) areas for statistical analysis. For each electrode position (frontal to parietal), we used separate Rm-ANOVAs to investigate main effects of timing (predictable vs. unpredictable) and laterality, and their interactions on the amplitude of the ERP responses to movement onset during each condition. In addition, we also used an Rm-ANOVA to investigate the main effect of electrode position on ERP responses to hand and speech movement separately. ERP responses were analyzed within 2 premotor and 10 post-motor time windows spanning from -100 ms before to 500 ms after hand and speech movement onset (each 50 ms long). For each time window, an Rm-ANOVA was used to examine the main effect of electrode position on ERP responses to hand and speech movement onset. Results of the analysis identified two major ERP response components: 1) a premotor ERP that started approximately -100 ms movement onset for both hand and speech, and 2) a post-motor ERP activity that followed hand and speech movement onset.

3.4.2.1 ERP Responses to Hand Movement

The temporal profiles of ERP responses to hand movement onset in four representative electrodes (F7, FCz, C1 and P5) are shown in Figure 3.2A. The topographical distribution maps of ERP activities within 50 ms long time windows from -200 ms before to 500 ms after hand movement onset are shown in Figure 3.2B. Results of the analysis revealed significant main effects of electrode position on ERP responses within time windows before and after hand movement onset (all p-values<0.05). We found a significant main effect of electrode position for time windows at -100 to -50 ms (F(5,77)=13.29, p<0.001, η²=0.42) and -50 to 0 ms (F(5,77)=34.23, p<0.001, η²=0.48) before
and 0 to 50 ms after hand movement ($F_{(5,77)}=8.49, p<0.001, \eta^2=0.37$). Post-hoc tests using Bonferroni’s correction revealed that for these time windows, the ERP responses were distributed with amplitudes predominantly larger over the parietal area (Figure 3.2B). For time windows after 50 ms following hand movement, we found that the ERPs were distributed with larger amplitudes over the central electrodes (all $p$-values<0.05). In addition, for electrodes over the medial parietal area (P3 and P4), results of the analysis revealed significant main effects of timing ($F_{(1,12)}=7.2, p<0.05, \eta^2_p=0.42$) and laterality ($F_{(1,12)}=10.54, p<0.01, \eta^2_p=0.55$), but no timing × laterality interaction ($F_{(1,12)}=1.38, p>0.1, \eta^2_p=0.10$) on ERP responses within the time window from -100 to -50 ms prior to hand movement onset. Moreover, results of the analysis for lateral parietal electrodes (P5 and P6) yielded significant main effects of timing ($F_{(1,12)}=5.01, p<0.05, \eta^2_p=0.31$) and laterality ($F_{(1,12)}=46.51, p<0.001, \eta^2_p=0.63$) with no timing × laterality interaction ($F_{(1,12)}=1.01, p>0.1, \eta^2_p=0.08$) on ERPs within -50 to 0 ms before hand movement onset. For the time window from 0 to 50 ms after hand movement onset, results only revealed a significant main effect of laterality ($F_{(1,12)}=9.75, p<0.01, \eta^2_p$). Post-hoc tests revealed that for both predictable and unpredictable conditions, ERP responses were left-lateralized over the medial and lateral parietal electrodes within time windows from -100 to -50 ms and -50 to 0 ms before and 0 to 50 ms after hand movement ($p<0.01$). In time windows from -100 to -50 and -50 to 0 ms before hand movement, ERP responses were significantly smaller ($p<0.05$) for temporally-predictable compared with unpredictable stimuli in the left medial parietal (P3) (see Figure 3.3A) and the left lateral parietal (P5) electrodes (see Figure 3.3B). No main effects of timing or laterality were found for the time windows after 50 ms following hand movement onset.
Figure 3.2 The temporal profile of ERPs and their topographical distribution maps in response to hand movement onset. A) displays the overlaid ERP profiles for predictable (red lines) and unpredictable (black lines) conditions in Frontal (F7), Frontocentral (FCz), Central (C1) and parietal (P5) electrodes from −200 ms before to 500 ms after the onset of the hand movement. B) illustrates the topographical distribution maps of ERPs in response to hand movement in 2 premotor and 10 post motor time windows (each 50 ms long) for predictable and unpredictable conditions separately. (Color figure online).
Figure 3.3 The bar plot representation of grand-average premotor ERP responses to hand movement onset for temporally-predictable vs. unpredictable condition. A) shows the grand-average ERP amplitudes over the left and right medial parietal electrodes (P3 and P4) for premotor activities at a time window from −100 to −50 ms before hand movement onset. B) shows the grand-average ERP amplitudes over the left and right lateral parietal electrodes (P5 and P6) for premotor activities at a time window from −50 to 0 ms before hand movement onset.

3.4.2.2 ERP Responses to Speech Production

The temporal profiles of ERP responses to speech movement onset in four representative electrodes (F7, FCz, C1 and P5) are shown in Figure 3.4A. The topographical distribution maps of ERP activities within 50 ms long time windows from -200 ms before to 500 ms after speech movement onset are shown in Figure 4B. We found that for all time windows spanning from -100 ms before to 500 ms after speech onset, the positive-polarity ERPs had a frontal distribution with and inversion (negative polarity)
over the posterior parietal areas (Figure 3.4B). No significant main effect of laterality was found for any of the tested time windows before and after speech movement (all $p$-values > 0.05).

However, at one time window from -100 to -50 ms before speech onset, we found an ERP component with negative polarity over the frontocentral electrode (FCz) that was significantly smaller in amplitude ($t_{(12)}=2.65, p<0.05, \eta^2=0.37$) for temporally-predictable compared with unpredictable stimuli (see Figure 3.5). No significant main effect of timing was found for other time windows or electrode positions in response to speech movement onset (all $p$-values > 0.1).

3.4.3 Correlation Analysis

We performed correlation analyses on the amplitudes of the ERP responses and the behavioral measures of reaction time for hand and speech movement in both predictable and unpredictable conditions. Correlations were performed on the mean amplitudes of the ERPs extracted within time windows from -100 ms before to 500 ms after the movement onset (10 ms time steps) and the reaction time measures for each timing and modality factor separately. Correlation results were corrected for multiple comparisons using Bonferroni’s method.

3.4.3.1 ERP Correlation with Hand Movement Reaction Time

We found three-time windows within which there were distinct differences in correlation measures between ERPs and hand movement reaction time for predictable vs. unpredictable conditions: 1) -40 to -30 ms before hand movement, 2) 130 to 140 ms, and 3) 180 to 190 ms after hand movement.
Figure 3.4 The temporal profile of ERPs and their topographical distribution maps in response to speech movement onset. A) displays the overlaid ERP profiles for predictable (red lines) and unpredictable (black lines) conditions in Frontal (F7), Frontocentral (FCz), Central (C1) and parietal (P5) electrodes from −200 ms before to 500 ms after onset of the speech movement. B) illustrates the topographical distribution maps of ERPs in response to speech movement in 2 premotor and 10 post motor time windows (each 50 ms long) for predictable and unpredictable conditions separately.
Figure 3.5 The bar plot representation of grand-average premotor ERP responses to speech movement onset for temporally-predictable vs. unpredictable condition. Bar plots show the grand-average ERP amplitudes over the frontocentral electrode (FCz) for premotor activities at a time window from −100 to −50 ms before speech movement onset.

For predictable condition, we found a significant negative correlation between ERP amplitudes at the left central electrode (C1) and reaction time ($r = -0.63$, $p < 0.05$; corrected) in only the pre-motor (-40 to -30 ms) time window relative to the onset of the hand movement. Figure 3.6A shows the overlaid correlation profiles for predictable and unpredictable conditions within -100 to 500 ms relative to hand movement onset in the left and right frontal (F1 and F2), central (C1 and C2) and medial parietal (P3 and P4) electrodes (filled circles indicate significant correlations: $p < 0.05$; corrected). In addition, a strong negative correlation between ERPs and reaction times was found in the time window from 130 to 140 ms at F1 (left frontal) electrode for predictable condition but this correlation did not reach a significant level ($r = -0.49$, $p > 0.05$). For unpredictable
condition, a significant negative correlation between ERP amplitude and hand movement reaction time was found at the right parietal electrode (P4) within the time window from 180 to 190 ms ($r=-0.6, p<0.05$; corrected). The topographical distribution maps for the results of our correlation analysis within the corresponding time windows are shown in Figure 3.6B.

Figure 3.6 A) Profiles of the correlation between ERP amplitudes and behavioral reaction times for hand movement onset overlaid across predictable and unpredictable conditions in the left and right frontal (F1 and F2), central (C1 and C2), and medial parietal (P3 and P4) electrodes. B) Topographical distribution maps of the correlation between ERP amplitudes in three-time windows (−40 to −30 ms, 130–140, and 180–190 ms) and behavioral reaction times for hand movement onset during temporally-predictable and unpredictable blocks.
3.4.3.2 ERP Correlation with Speech Movement Reaction Time

For speech movement onset, distinct differences between correlation measures of ERP and reaction time were observed within one pre-motor (-40 to -30 ms) and one post-motor (50 to 60 ms) time windows for predictable and unpredictable conditions. We found that ERP amplitude at the left frontal (F1) electrode was negatively correlated with speech movement reaction time for predictable condition in the -40 to -30 ms time window ($r = -0.81 \ p<0.01$; corrected). Figure 3.7A shows the overlaid correlation profiles for predictable and unpredictable conditions within -100 to 500 ms relative to speech movement onset in the left and right frontal (F1 and F2), central (C1 and C2) and parietal (P3 and P4) electrodes. Moreover, for predictable condition, the mean amplitude of ERPs at the right central (C2) electrode was negatively correlated with the reaction time for speech movement within a time window from 50 to 60 ms ($r=-0.63, \ p<0.05$). The topographical distribution maps for the results of our correlation analysis within the corresponding time windows are shown in Figure 3.7B.

3.5 Discussion

The present study investigated the effect of stimulus temporal predictability on behavioral and neural responses associated with speech and hand movement. Our experimental design provided a novel method to test the hypothesis that motor responses in speech and hand modalities are facilitated by a predictive coding mechanism to produce faster movements in response to temporally-predictable sensory stimuli. We also explored the neural mechanisms of the predictive coding model by measuring ERPs in response to movements during predictable and unpredictable conditions.
Figure 3.7 A) Profiles of the correlation between ERP amplitudes and behavioral reaction times for speech movement onset overlaid across predictable and unpredictable conditions for the left and right frontal (F1 and F2), central (C1 and C2), and parietal (P3 and P4) electrodes. B) Topographical distribution maps of the correlation between ERP amplitudes in two-time windows (−40 to −30 ms and 50–60 ms) and behavioral reaction times for speech movement onset for predictable and unpredictable conditions.
Our data suggested that premotor ERP activities serve as a robust neurophysiological biomarker of the predictive coding mechanism, as indexed by their suppression as well as their strong correlation with movement reaction time during predictable compared with unpredictable stimulus timing condition. In the following sections, findings are discussed with the goal to provide a unified framework for understanding the temporal processing mechanisms in the motor system.

3.5.1 Effects of Stimulus Timing on Movement Reaction Time

Analysis of behavioral responses confirmed our hypothesis regarding the effect of stimulus temporal predictability on motor reaction time. We found that motor responses in both speech and hand modalities were significantly faster for temporally-predictable compared with unpredictable stimuli. In addition, we observed that button press responses of the hand were significantly faster than speech production of the vowel sounds regardless of stimulus timing condition. These findings are consistent with findings of previous studies (Bevan et al., 1965; Vallesi, McIntosh, Shallice, et al., 2009) and provide further support for a predictive coding mechanism that enables the motor system to process temporal regularity (predictability) to generate faster movements. In the context of the internal forward model theory (Witney et al., 1999; Wolpert, 1997; Wolpert et al., 2011; Wolpert & Flanagan, 2001; Wolpert et al., 2001), we propose that temporally-predictable sensory stimuli result in the establishment of more robust feedforward motor representations during movement. As suggested by previous studies (Miall & Wolpert, 1996; Wolpert & Flanagan, 2001), the internal forward model can learn, reinforce and internally simulate temporal relationships between motor commands.
and sensory stimuli. Based on our findings, we propose that feedforward motor mechanisms are enhanced, and the contribution of sensory feedback is reduced for processing temporally-predictable stimuli, leading to faster movement with shorter reaction times. Moreover, modality-specific modulation of reaction time with faster responses for hand movement can be explained by findings of previous studies (Gajewski & Falkenstein, 2013; Ma & Trombly, 2004), suggesting that more complex movements such as those in speech require a longer time for coordination of movement in a large group of respiratory and laryngeal muscles for vowel vocalization.

3.5.2 Effects of Stimulus Timing on ERP Responses

Results of the ERP analysis led to the identification of a premotor and postmotor neural response components that emerged before and after speech and hand movement onsets, respectively. We found that the premotor component of ERPs was elicited at approximately -100 ms before movement onset. For hand movement, the premotor ERPs had a left-lateralized distribution with stronger activations over the medial parietal (P3) and lateral parietal (P5) electrodes. However, for the speech production task, premotor ERPs were not lateralized and were distributed with stronger activities over the frontocentral (F1 and F2) electrodes. We found that the premotor component of ERPs in a time window from -100 to -50 ms before movement onset was significantly suppressed in response to temporally-predictable compared with unpredictable stimuli for both speech and hand modalities. However, no effect of stimulus timing was found on postmotor ERP responses.
The suppression of premotor neural activities in response to temporally-predictable stimuli in the present study can be discussed in the framework of the internal forward model (Witney et al., 1999; Wolpert et al., 2011; Wolpert & Flanagan, 2001). According to this model, the efference copies of motor commands are translated into internal predictions that estimate the current and future states of the motor system and make adjustments when errors occur in sensory feedback associated with self-generated movements. Studies have demonstrated that these internal predictive signals can suppress neural activities in response to sensory stimuli triggered by button press (Chen et al., 2012; Mifsud et al., 2016; Timm et al., 2016) or self-produced speech (Aliu, Houde, & Nagarajan, 2009; Behroozmand & Larson, 2011; Behroozmand et al., 2011; Behroozmand et al., 2016; Chang et al., 2013; Heinks-Maldonado, Mathalon, Gray, & Ford, 2005; Ventura, Nagarajan, & Houde, 2009). This motor-induced suppression effect has been proposed to account for a reduced contribution of sensory mechanisms for processing incoming stimuli, as indexed by the attenuation of auditory neural activities during active vocalization compared with passive listening to the playback of the same self-produced vocalizations (see Behroozmand et al., 2011). In addition, other studies have provided evidence that the internal predictive signals may enhance temporal processing of sensory information (Conradi et al., 2016), and lead to greater suppression of neural activities in response to temporally-predictable compared with unpredictable sensory stimuli (Behroozmand et al., 2011; Behroozmand et al., 2016; Chen et al., 2012). These findings indicate that during movement, a more robust temporal predictive code can be established internally to provide an accurate estimate of timing for sensory stimuli that follow a temporally-regular (predictable) pattern. The behavioral consequence of this
effect is to drive motor behavior with shorter reaction times in response to temporally-predictable compared with unpredictable sensory stimuli (Bevan et al., 1965; Niemi & Naatanen, 1981; Vallesi, McIntosh, Shallice, et al., 2009).

In this study, we provide supporting evidence for a temporal predictive code in the motor system by showing that the ERP correlates of premotor neural activities were modulated by the temporal dynamics of externally-presented visual cue stimuli. Our data showed that the left-lateralized premotor ERP activities over the parietal area during hand movement, and premotor ERP activities over the frontocentral area during speech production were significantly suppressed in response to temporally-predictable compared with unpredictable stimuli. These findings are consistent with the results of a previous study (Baker et al., 2012), and suggest that distinct neural networks are involved in temporal processing during hand and speech movement. Previous studies have suggested that networks within the parietal lobe and cerebellum provide a neural substrate for temporal information processing during hand movement control (Blakemore & Sirigu, 2003). Moreover, it has been demonstrated that premotor ERP activities over the parietal area encode the level of expectancy and temporal predictability for hand motor responses (Roux, Mackay, & Riehle, 2006). When the time interval between a warning and an imperative signal was predictable, the brain could more accurately estimate the timing of upcoming future stimuli and facilitate movement production for predictable conditions. In this study, predictable stimuli provided a higher level of expectancy and conveyed more predictive information about the timing of next movement induced by sensory cues, which were accompanied by shorter reaction times and decreased amplitude of premotor neural activities. In contrast, unpredictable stimuli conveyed less predictive information.
and were associated with a smaller degree of premotor neural response attenuation over the parietal electrodes during the button press task. We propose that suppression of premotor activities for predictable condition over the left parietal electrodes in this study may reflect parietal lobe activities involved in temporal processing of sensory stimuli during hand movement. In addition, we suggest that the parietal activities are indicative of sensorimotor integration and internal predictive coding mechanisms during hand movement.

In the speech modality, our data showed suppression of frontocentral premotor activities in response to temporally-predictable vs. unpredictable stimuli suggesting that this area may play a critical role in temporal information processing during speech. It has been previously shown that the N1 and P2 ERP components over the frontocentral electrodes were suppressed in response to temporally-predictable compared with unpredictable speech stimuli (Behroozmand et al., 2016). Converging evidence suggests that the suppression of frontocentral neural activities for predictive motor timing of speech reflects brain mechanisms that are involved in extracting temporal regularities from incoming sensory stimuli to adjust speech motor commands for effective verbal communication. We propose that the sensorimotor integration mechanisms of speech are responsible for suppression of neural activities for temporally-predictable sensory stimuli that are encoded by the internal feedforward neural representations. However, unpredictable stimuli with irregular temporal dynamics require the allocation of more neural resources to process sensory information for speech motor production.

An alternative interpretation of the observed suppression effect during predictable conditions is that in addition to sensorimotor processes, higher level cognitive
mechanisms may also be involved in processing temporal information during movement production. Findings from previous studies have suggested that uncertainty in sensory stimuli increases the need for more cognitive resource to process information during movement production (Dieterich, Endrass, & Kathmann, 2016), which leads to an increase in the amount of neural activities generated by the brain (Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005). Based on our findings, we propose that after a predictive code is established for temporally-predictable stimuli, association between warning (cue) and imperative (go) signals is mediated by automatic processes that demand less effort and cognitive loads for processing. However, for temporally-unpredictable stimuli, the brain has to deal with a greater degree of uncertainty, which calls for assigning more cognitive resources and subsequently stronger neural activities for processing temporal information for movement production. In this context, suppression of neural activities in response to predictable stimuli is an indication of a reduced degree of cognitive load for temporal information processing during movement production. In addition, in the context of a predictive model of hazard function, an increased sense of expectancy about an imperative event evolves as a function of the elapsed time (Coull et al., 2016). It has previously been shown that the left inferior parietal cortex preferentially responds to temporally-predictable stimulus patterns, and the activity in this area tracked the evolving temporal probability of the hazard function during hand movement (Coull et al., 2016). We propose that our findings related to timing-dependent modulation of premotor ERPs in the left parietal area may reflect neural mechanisms of hazard function during hand movement.
3.5.3 ERP Correlates of Movement Reaction Time

Results of the correlation analysis provided support for our hypothesis that for predictable sensory stimuli, the brain can extract information about the relationship between temporally-regular sensory input and motor commands. This hypothesis was confirmed by our data indicating a significant correlation between movement reaction time of both speech and hand modalities and the amplitude of premotor and postmotor ERP activities during the temporally-predictable condition. Based on this finding, we propose that the ERP responses to movement during predictable condition are neurophysiological biomarkers of temporal information processing and can be used to predict reaction time during speech and hand movement tasks.

For hand modality, a significant negative correlation was found between the amplitude of the left central electrode (C1) and reaction time for predictable condition at a time window from -40 to -30 ms prior to hand movement onset. Predictable reaction time for speech was negatively correlated with the ERP amplitude in electrodes over the left frontal (F1) and bilateral parietal (P3 and P4) regions at the same time window from -40 to -30 ms before movement onset. These negative correlation measures suggest that larger ERP amplitudes are associated with shorter movement reaction time in response to temporally-predictable stimuli. We proposed that the increase in premotor ERP activities at -40 to -30 ms before movement onset highlights neural mechanisms that extract temporal regularities from sensory stimuli to drive faster movements in response to behaviorally-relevant sensory cues. Moreover, we propose that predictive motor timing enhances neural communication and temporal synchrony between sensorimotor networks involved in movement production leading to faster motor reaction times. The significant
negative correlation at the time window within -40 to -30 ms may indicate that the motor system incorporates an internal predictive code to more accurately estimate and respond to temporally-predictable sensory stimuli.

Findings of our study also suggest that larger neural response amplitudes at -40 to -30 ms time window may reflect a higher degree of sensorimotor integration which can lead to faster movement for predictable sensory stimuli. We found that the speech modality exhibited stronger premotor correlations than the hand modality, suggesting that temporal information about predictable sensory stimuli may be more accurately encoded by the speech compared with the hand motor system. Furthermore, we propose that different neural substrates subserve predictive coding mechanisms for hand and speech, as indexed by our findings showing a distinctly different pattern of correlations in these two modalities. We also found a negative correlation between postmotor ERP responses in the right parietal electrode (P4) and reaction time for unpredictable hand movement condition at a time window from 180 to 190 ms after movement onset. For speech production, ERP responses for predictable condition were found to be negatively correlated with reaction time over the right central (C2) electrode at time window from 50 to 60 ms after speech onset. These postmotor correlations might indicate the dynamic nature of the internal feedforward model, suggesting that even during movement execution, the feedforward motor commands may generate estimations to process timing information for the next movements induced by temporally-predictable sensory stimuli.
Chapter 4

Functional Dissociation of Temporal Processing Mechanisms during Speech Production and Hand Movement: An ERP Study

---

4.1 Abstract

Skilled motor actions are mediated by neural mechanisms that incorporate sensory feedback for driving or suppressing movement with remarkable temporal precision. The predictive coding model proposes that the brain performs this function by establishing an internal representation of timing to accelerate movement response time. However, it is unclear whether different neural mechanisms are involved in temporal processing of movement initiation and cessation. The present study examined how temporal information is encoded for initiation and cessation of speech and hand movement. Event-related potentials (ERPs) were recorded while young healthy subjects performed speech and hand movement initiation and cessation in response to temporally predictable and unpredictable visual stimuli. We found that predictable stimuli elicited faster movement in both speech and hand modalities, with shorter reaction times associated with movement cessation compared with initiation. Analysis of ERPs revealed that premotor neural activities were significantly attenuated before speech initiation and hand movement initiation and cessation for temporally predictable vs. unpredictable conditions, but an opposite pattern was observed for speech cessation. In addition, we observed that the premotor ERPs were significantly modulated during speech initiation vs. cessation, but no such effect was found during hand movement. Finally, we found that the premotor ERPs were strongly correlated with motor reaction time during movement initiation and cessation for speech and hand modalities only in response to temporally predictable stimuli. These findings indicate that premotor ERPs reflect a temporal predictive code for planning of movement initiation and cessation and highlight
functional dissociation of temporal processing mechanisms in speech and hand motor systems.

4.2 Introduction

The production and control of voluntary movement is an important function of the nervous system that enables humans and animals to interact with their environment. This critical function is mediated by complex neural mechanisms that incorporate sensory information to drive or suppress future motor actions. A fundamental aspect of sensorimotor processes underlying movement is to respond to sensory cues with an extremely high temporal precision. This capability is even more crucial for planning and execution of movement when the timing of sequential muscle activation (or deactivation) needs to be finely controlled for performing a goal-directed movement (e.g., driving, playing tennis, speaking, etc.). To accomplish such remarkable temporal precision, the brain has to optimally control movement reaction times for generating or suppressing motor responses to behaviorally relevant sensory stimuli. Although this inherent property of the sensorimotor system is crucial for survival, the underlying neural mechanisms of temporal processing during movement are not clearly understood. Therefore, the present study was motivated by the question as to what the neural correlates of temporal processing mechanisms for movement initiation and cessation are and how these neural processes are influenced by timing information embedded in external sensory stimuli.

The sensory processing of timing information has been previously studied using the odd-ball paradigm by showing that the auditory system extracts the patterns of temporal regularity in stimuli with predictable duration and time intervals, and it elicits
a mismatch negativity (MMN) response when a deviant stimulus violates the established temporal predictive pattern (Cornella et al., 2012; Moberget et al., 2008; Näätänen et al., 2007; Schwartz et al., 2011; Symonds et al., 2016; Toyomaki et al., 2008; van Zuijen et al., 2005; Waongne et al., 2012). Other studies have investigated the sensorimotor processing of temporal information by using the foreperiod (FP) paradigm in which the time interval between a prepare (prepare) and an imperative signal is manipulated while subjects perform a motor response reaction time task (Bevan et al., 1965; Drazin, 1961; Johari, den Ouden, & Behroozmand, 2018; Karlin, 1959; Klemmer, 1956; Mattes & Ulrich, 1997; Niemi & Naatanen, 1981; Timm et al., 2016; Vallesi, McIntosh, Shallice, et al., 2009). Findings of these studies have indicated that for temporally predictable (fixed duration) FPs, motor response reaction time for movement initiation was significantly shorter (faster movement), and movements were performed with greater temporal precision compared with those in response to unpredictable FPs with variable duration. These results support the notion that temporal predictability of sensory stimuli can facilitate motor function for driving faster movements, however, the underlying neural mechanisms of this effect remains to be elucidated.

In addition to studying movement initiation mechanisms (e.g., starting a hand motor response), more recent studies have investigated the underlying mechanisms of movement inhibition during tasks that involved withholding prepared motor actions in response to inhibitory cue signals (Berchicci, Lucci, Spinelli, & Di Russo, 2015; Morein-Zamir, Chua, Franks, Nagelkerke, & Kingstone, 2007). Results of these studies have shown that motor response reaction time was decreased, and movement was executed faster as temporal predictability of inhibitory cue signals was increased, suggesting that
temporal predictability of sensory stimuli can modulate movement inhibition
mechanisms. Although these findings suggest temporal-specific effects of sensory stimuli
on movement reaction time, there are still aspects of movement mechanisms that have
remained relatively unexplored in this line of work. As an example, there is lack of
knowledge about the effects of temporal information on movement mechanisms
implicated in stopping (terminating) an ongoing motor action (e.g., hand movement or
speech production). Hereafter, this latter motor response (i.e., stopping an ongoing
movement) will be referred to as movement cessation in this paper, which is different
from movement inhibition mechanisms investigated in previous studies (Berchicci et al.,
2015; Morein-Zamir et al., 2007).

In this study, we aimed to examine the effects of temporal predictability of
sensory stimuli on neural mechanisms of movement initiation and cessation in the speech
and hand motor systems. This work was motivated by a recent study in our lab (Johari &
Behroozmand, 2017b) in which we designed an experimental paradigm to simultaneously
measure motor response reaction times during initiation and cessation of speech and hand
movements while subjects were cued to press a button or vocalize a steady vowel sound
in response to a go signal, and stop their ongoing motor action in response to a stop
signal. Results of that study (Johari & Behroozmand, 2017b) revealed that motor reaction
time during both speech and hand movement initiation and cessation was significantly
shorter in response to temporally predictable compared with unpredictable sensory
stimuli (i.e. go-stop cues). According to recent models of movement control (Wolpert et
al., 2011; Wolpert & Flanagan, 2001; Wolpert et al., 2001; Wolpert & Miall, 1996), our
earlier findings (Johari & Behroozmand, 2017b) were consistent with the notion that the
brain can internally simulate the behavior of the motor system during planning, execution and control of movement. According these models, the brain can learn the association between motor commands and expected sensory consequences of the movement and establish a predictive code for the next state of the movement. In the context of this model, extracting timing information from external cues may lead to establishing a predictive coding that fine tune motor commands and drive faster movement in responses to temporally predictable sensory stimuli. Although such a temporal predictive mechanism is implicated in a wide range of motor behaviors that are crucial for our survival, our knowledge about the neural mechanisms of such remarkable functionality in the sensorimotor system is relatively poor.

Novel insights into the underlying neural correlates of temporal processing mechanisms during movement initiation have been provided by neuroimaging studies that indicated functional disassociation between brain regions involved in processing sensory stimuli with predictable vs. unpredictable temporal patterns (Thickbroom et al., 2000; Vallesi, McIntosh, Shallice, et al., 2009; Vallesi et al., 2007). These studies have shown that neural activities in the caudal portion of supplementary motor area (SMA) (Thickbroom et al., 2000), as well as the right dorsolateral prefrontal cortex (DLFPC) (Vallesi, McIntosh, Shallice, et al., 2009; Vallesi et al., 2007), and the left inferior parietal cortex (IPC) (Coull et al., 2016) were significantly stronger when movements were initiated in response to temporally unpredictable compared with predictable stimuli. In addition, single unit recordings from medial premotor cortex (MPC) in monkeys have shown that neurons in this area not only encode temporally predictable intervals in sensory stimuli, but are also activated to generate timed intervals during rhythmic
movements (Crowe et al., 2014; Merchant et al., 2015; Merchant, Pérez, et al., 2013). This evidence suggests that premotor neurons are core components of a timing network that uses interval tuning to process temporal regularity in sensory stimuli during a variety of behaviorally relevant motor tasks. These findings further support the existence of specialized neural networks that process timing information during movement production. Similarly, studies have found distinct patterns of brain activations in response to predictable vs. unpredictable sensory stimuli that cued hand movement inhibition during a button press task (Leunissen, Coxon, & Swinnen, 2016; Vink et al., 2005). Findings of these studies have revealed that the striatum was more strongly activated as the temporal predictability of the inhibitory cue signals was increased (Vink et al., 2005). In addition, it has also been shown that when subjects performed hand movement inhibition during a stop signal task, two distinct areas in the basal ganglia were differentially activated in response to frequent vs. infrequent stop trials (Leunissen et al., 2016). Findings of this latter study showed that the areas within the subthalamic nucleus (STN) and anterior striatum exhibited greater activations when stop signals were presented infrequently (unpredictable), whereas greater activations were observed in the caudate nucleus when stop signals followed a frequent (predictable) pattern. These findings suggest that initiation of movement is primarily mediated by neural networks within the cortical motor regions (e.g., DLPFC, SMA, and MPC), whereas movement inhibition is controlled by subcortical structures such as those in the basal ganglia network.

Although stimulus temporal predictability was shown to modulate neural activities after the movement initiation and inhibition, a number of studies have reported
that neural activities prior to movement initiation (Alegre et al., 2003; Baker et al., 2012; Berchicci et al., 2015; Kuhn et al., 2004) and inhibition (Berchicci et al., 2015) are also modulated in response to temporally predictable vs. unpredictable sensory stimuli. Electroencephalography (EEG) recordings in humans have demonstrated that the pre-movement neural activities were elicited up to two seconds before the onset of motor responses and were found to be stronger in scalp electrodes over the bilateral frontal areas (Baker et al., 2012). In a follow-up work to our original study on temporal predictive mechanisms of speech and hand movement (Johari & Behroozmand, 2017b), we also examined the neural correlates of movement initiation in response to predictable and unpredictable stimuli using event-related potential (ERP) activities that were extracted from EEG signals recorded during the performed motor reaction time tasks (Johari & Behroozmand, 2017a). In that study (Johari & Behroozmand, 2017a), we identified premotor ERP activities over the frontal and parietal areas, which were elicited 100 ms before speech and hand movement initiation and were significantly attenuated in response to temporally predictable compared with unpredictable sensory stimuli. Although the nature of such premotor neural activity attenuation is not fully understood, one possible interpretation of this effect is that the attenuation of premotor ERPs may be accounted for by modulation of neural processes that underlie predictive coding mechanisms during movement. For temporally predictable stimuli, the fixed timing interval between the prepare and go cues could potentially be more accurately extracted for driving motor commands compared to that for unpredictable stimuli with randomized timing intervals. Thus, the attenuation of ERP activities in response to temporally predictable stimuli may in fact represent a more accurately established predictive code for
speech and hand movement in response to fixed timing intervals. In addition, we found that the amplitude of the premotor ERPs was negatively correlated with speech and hand motor reaction time during movement initiation, with a stronger correlation for temporally predictable stimuli. These findings indicated that the premotor ERPs are robust neurophysiological biomarkers of speech and hand motor reaction time and are modulated by stimulus temporal predictability.

Although previous studies have provided insights into the neural mechanisms of temporal information processing during movement initiation and inhibition, our understanding about these mechanisms has been limited by several factors. First, previous studies have primarily focused on examining the effects of temporal predictability on neural mechanism of movement initiation and inhibition and less is known about the mechanism of movement cessation during an ongoing motor action. Second, previous research has primarily focused on studying the neural correlates of movement initiation and inhibition after (but not before) the onset of motor responses, and therefore, it is unclear how temporal predictability of sensory stimuli affects premotor mechanisms of movement planning. Third, previous studies have mainly examined motor responses during hand movement initiation (Alegre et al., 2003; Kuhn et al., 2004) or inhibition (Berchicci et al., 2015), and therefore, it is not well-understood how the observed effects on hand movement may generalize to other modalities such as the speech motor control system. Lastly, previous studies have not provided an account for possible interactions between movement mechanisms in hand and speech modalities. In fact, it is still unclear to what extent speech production and hand movement share
common mechanisms, and how temporal features of sensory stimuli are encoded by these
two different motor control systems.

In our previous study (Johari & Behroozmand, 2017a), we examined premotor
neural correlates of temporal predictive coding mechanisms for speech and hand
movement initiation. The present study was motivated by the question whether the
premotor neural correlates of movement cessation differ from those of movement
initiation, and how premotor neural activities are modulated by predictability of external
sensory stimuli during speech production and hand movement. Therefore, in the present
study, we conducted a more systematic examination to determine possible interactions
between movement initiation and cessation mechanisms in the speech and hand motor
systems in response to temporally predictable and unpredictable sensory stimuli. As
detailed in our previous studies (Johari & Behroozmand, 2017a, 2017b), the experimental
paradigm involved randomized initiation and cessation of steady vowel vocalization
(speech) and button press (hand movement) tasks, which were cued by visually presented
“go” and “stop” signals. The experiment consisted of two counterbalanced blocks in
which the timing between visual cues (prepare, go and stop signals) was either temporally
predictable (fixed interval) or unpredictable (variable interval). This experimental design
allowed us to simultaneously examine movement initiation and cessation mechanisms in
a unified experimental framework, and to investigate the effects of stimulus temporal
predictability on motor mechanisms of speech and hand modalities. In this study, we
mainly focused on studying the relationship between the behavioral measures of reaction
time and premotor ERP activities elicited before speech and hand movement initiation
and cessation. The premotor component of ERP has been suggested to be the neural
signature of a temporal predictive code during the planning phase of the movement (Johari & Behroozmand, 2017a). Based on this notion, we hypothesized that premotor ERP activities would be elicited before movement initiation and cessation, and their modulation by stimulus temporal predictability would reflect a predictive code in the preparatory phase of speech and hand movement. In addition, based on supporting evidence from previous studies (Alegre et al., 2003; Berchicci et al., 2015; Johari & Behroozmand, 2017a), we hypothesized that modulation of premotor neural activities would be correlated with temporal-specific changes in the behavioral measures of motor reaction time in the speech and hand modalities. Finally, based on our earlier findings related to differential effects of temporal predictability on motor reaction times during movement initiation and cessation (Johari & Behroozmand, 2017b), we hypothesized that premotor neural responses of movement cessation would be modulated differently by the temporal predictability of sensory stimuli compared with those for movement initiation.

To address these hypotheses, the present study focused on examining the effects of stimulus temporal predictability and movement initiation and cessation on premotor components of neural activities in speech and hand motor systems. Although the primary objective of this study was to examine premotor neural activities, we took an exploratory approach to examine the effects of stimulus temporal predictability on neural activities after movement initiation and cessation in speech and hand motor systems.

4.3 Methods and Materials

4.3.1 Subjects

A total of 20 subjects (9 males and 11 females, age range 20-30 years old) participated in this study. Subjects in this study included 13 subjects who participated in
studies presented in chapters 2 and 3, and 7 additional subjects were recruited in the present study to increase the sample size and the power of our statistical analysis. Subjects reported no history of psychiatry and neurological conditions and they had no history of speech or hearing impairment. All subjects also had normal vision. Handedness of subjects obtained using Edinburg handedness inventory (Oldfield, 1971), and they were right handed (score range 72-100). All study procedures, including recruitment, data acquisition and informed consent were approved by the University of South Carolina Institutional Review Board, and subjects were monetarily compensated for their participation.

4.3.2 Experimental Design

The experiment was conducted in a sound attenuated booth in which subjects performed the experimental tasks while the EEG signals were recorded. Subjects were instructed to prepare to initiate speech or hand movement following the onset of a relevant face or hand picture on the screen (prepare signal) and start vocalizing a steady vowel sound /a/ or pressing a button after a circle (go signal) appeared on the screen, and stop the vocalization or release the button after the circle disappeared (stop signal) (see figure 2.1, chapter 2). The order of response modalities (speech vs. hand) was randomized to control the priming effects on response time. Subjects were seated in a comfortable chair directly in front of the computer screen at a distance about 15-20 inches to easily see the presented visual cues (prepare, go and stop signals). The background of the screen was black, and the visual cues appeared as white circles at 1.5
inches in diameter. We designed two counterbalanced blocks within which subjects were asked to respond to the speech and hand movement visual cues in a randomized order: 1) temporally predictable block, in which there was a fixed time interval of 1500 ms between the onset of the prepare and go signals, as well as the go and stop signals, and 2) temporally unpredictable block in which the time interval between the prepare and go signals, as well as the go and stop signals, was randomized between 1000-2000 ms. During each block, a total number of 220 trials were collected, with approximately 110 trials for speech and hand movement initiation and cessation conditions. The inter-trial-interval (ITI) was 2-3 seconds in each block and subjects took 5 minutes break between two blocks. The total duration of the experiment was approximately 1 hours, with 30 minutes for completion of each block. All the experimental parameters, including the presentation of prepare, go, and stop signals and the time intervals between them were controlled by a custom-made program implemented in Max 5.0 (Cycling ’74, San Francisco, CA). Additionally, timing within trials (T) and order of trials (speech and hand) were controlled by the Max program. The speech signal was recorded through a head-mounted AKG condenser microphone (model C520) amplified by a Motu Ultralite-MK3 module. The initiation and cessation of vocalizations were marked by TTL pulses that were generated by a voice onset/offset detector algorithm in Max 5.0 applied to subjects’ speech signal. Max 5.0 also generated TTL pulses for initiation and cessation of subjects’ button press. These TTL pulses were simultaneously recorded with EEG signals for time-locked averaging of ERP activities, and the analysis of behavioral measures of reaction time in each experimental condition.
4.3.3 Reaction Time Analysis

For each subject, measures of reaction time were obtained for both predictable and unpredictable blocks (button press initiation and cessation, speech initiation and cessation). The reaction time for each condition was extracted using a custom-made MATLAB code by calculating the time difference between the onset of the go and stop signals and the initiation and cessation of speech and hand movements, respectively. A repeated-measures analysis of variance (RANOVA) has been performed to test the main effects of predictability (timing), modality (speech and button press) and task (initiation and cessation) or interactions between these factors. If interactions were significant, pairwise comparisons were performed using post-hoc t-tests with Bonferroni’s correction for multiple comparisons (p<0.05).

4.3.4 EEG Data Acquisition

The EEG signals were recorded from 64 sites on the subjects’ scalp using the Brain Vision active electrode system (Brain Products GmbH, Germany) placed on a standard electrode cap (Easy-Cap GmbH, Germany). The electrode placement on the cap followed the standard 10-20 montage and the EEG signals were recorded using a common reference. A BrainVision actiCHamp amplifier (Brain Products GmbH, Germany) on a computer utilizing Pycorder software recorded the EEG signals at 1 kHz sampling rate after applying a low-pass anti-aliasing filter with 200 Hz cut-off frequency.
4.3.5 EEG Analysis

The EEGLAB toolbox (Delorme & Makeig, 2004) was used to analyze recorded EEG signals in order to extract ERPs time-locked to the onset of speech and hand movement initiation and cessation in response to temporally predictable and unpredictable stimuli. The recorded EEGs were first filtered offline using a band-pass filter with cut-off frequencies set to 1 and 30 Hz (−24 dB/oct) and then segmented into epochs ranging from −200 ms before and 500 ms after the initiation and cessation of the hand and speech movement. Following segmentation, artifact rejection was carried out to remove muscle and eye-blink activities by excluding epochs with EEG amplitudes exceeding ±50 μV. Individual epochs were then subjected to baseline correction by removing the mean amplitude of the pre-stimulus time window from −200 to -100 ms for each electrode. The extracted epochs were then averaged across all trials separately for each condition to obtain ERP activities for hand and speech movement initiation and cessation. A minimum number of 100 trials for each condition were used to calculate ERP activities for each individual subject. The extracted ERP components in response to speech and hand movement initiation and cessation were separately analyzed within 14 regions of interests (ROIs) that included electrodes over the left and right frontal (left: F1, F3, F5; right: F2, F4, F6), frontocentral (left: FC1, FC3, FC5; right: FC2, FC4, FC6), frontotemporal (left: FT9, FT7, F7; right: FT10, FT8, F8), central (left: C1, C3, C5; right: C2, C4, C6), centroparietal (left: CP1, CP3, CP5; right: CP2, CP4, CP6), parietal (left: P1, P3, P5; right: P2, P4, P6), and temporoparietal (left: TP9, TP7, P7; right: TP10, TP8, P8) areas (Figure 4.1). In each ROI, ERP amplitudes were extracted for 1 premotor (-100 to 0 ms) and 5 post-motor (0 to 500 ms) time windows with 100 ms duration. For each
time window, neural activities were measured as the mean amplitude of ERPs for all time points within a time window in three electrodes in the left (e.g., left frontocentral: FC1, FC3 and FC5) and three electrodes in the contralateral right side (e.g., right frontocentral: FC2, FC4 and FC6). Then, the extracted ERP profiles for each ROI were averaged across all subjects to calculate the grand-average ERP activities within 6 different time windows. We included laterality (left vs. right hemisphere) as a factor to examine whether speech and hand movement initiation and cessation are driven by lateralized or bilateral neural mechanisms in the brain. Within each time window, a four-way repeated-measures ANOVA was used for all ROIs to examine the main effects of stimulus timing (predictable vs. unpredictable), modality (speech vs. hand), task (initiation vs. cessation), and laterality (left vs. right) on ERP amplitudes. The analysis was corrected for the number of ROIs using Bonferroni’s correction for multiple comparisons (p<0.05).

Figure 4.1 Regions of interest (ROIs) for ERP analysis.
4.3.6 Correlation Analysis

We performed correlation analysis on the mean of ERP amplitudes in each ROI and the mean of reaction times for initiation and cessation of speech and hand movement in response to temporally predictable and unpredictable stimuli. Correlations were performed for each ROI using Bonferroni’s correction on the mean amplitudes of the ERPs extracted within time windows from -100 ms before to 500 ms after movement initiation and cessation onset (time steps: 100 ms), and the reaction time measures for speech and hand modalities. For significant correlations, we compared the mean of correlation coefficients in ROIs using Fisher’s transformation to determine whether correlation coefficients were statistically different for predictable vs. unpredictable conditions.

4.4 Results

4.4.1 Reaction Time Results

The means and standard deviations of motor reaction times for speech and hand movement initiation and cessation in response to temporally predictable and unpredictable stimuli are reported in Table 4.1. In the following section, results of significant main effects and interactions are reported for the behavioral measures of reaction time. The Rm-ANOVA analysis with timing (predictable vs. unpredictable), modality (speech vs. hand), and task (initiation vs. cessation) factors revealed a significant main effect of timing ($F_{(1, 19)} = 14.36, p = 0.02$), indicating shorter motor reaction time (faster movement) in response to temporally predictable compared with unpredictable stimuli, regardless of response modality and task. We also found a
significant main effect of modality ($F_{(1,19)} = 22.52, p < 0.0001$), indicating shorter motor reaction times (faster responses) in hand compared with speech motor system. Finally, we found that speech and hand motor reaction times were significantly shorter (faster responses) ($F_{(1,19)} = 57.26, p < 0.0001$) for movement cessation in comparison with initiation in response to both predictable and unpredictable stimuli. Finally, behavioral analyses did not yield any significant interactions between factors ($ps > 0.05$).

Table 4.1 The means and standard deviations of motor reaction times in milliseconds for two timing (predictable vs. unpredictable) conditions and two tasks (initiation vs. cessation), separately for speech and hand modalities.

<table>
<thead>
<tr>
<th></th>
<th>Predictable</th>
<th>Unpredictable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initiation</td>
<td>Cessation</td>
<td>Initiation</td>
</tr>
<tr>
<td><strong>Speech</strong></td>
<td>410 ± 101</td>
<td>327 ± 67</td>
<td>442 ± 71</td>
</tr>
<tr>
<td><strong>Hand</strong></td>
<td>357 ± 80</td>
<td>294 ± 63</td>
<td>388 ± 48</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>386 ± 87</td>
<td>331 ± 66</td>
<td>415 ± 66</td>
</tr>
</tbody>
</table>

4.4.2 ERP Activities for Speech Production and Hand Movement

The topographical distribution maps revealed prominent premotor ERP activities over the frontocentral and parietal electrodes for speech initiation (Figure 4.2A), and over frontal, centro-parietal, and parietal electrodes for speech cessation (Figure 4.2B). For hand initiation and cessation (Figures 4.3A and 4.3B), the topographical distribution maps showed prominent premotor ERPs over the bilateral frontal, central, and left parietal electrodes. In the following section, significant main effects and interactions are reported for ERPs in response to speech and hand movement initiation and cessation.
during temporally predictable and unpredictable blocks. ERP analyses were corrected for the number of ROIs using Bonferroni’s correction for multiple comparisons (p<0.05).

Statistical analysis of premotor ERPs (time window: -100 to 0 ms) in frontal and fronto-central regions revealed a significant main effect of timing (F(1,19) > 6.26, p < 0.02), indicating larger neural activities in response to temporally unpredictable compared with predictable stimuli before speech (Figure 4.4A) and hand movement (Figure 4.5A). In addition, we found that a significant main effect of modality (F(1,19) > 8.29, p < 0.01), indicating that premotor ERPs were larger for hand vs. speech movement regardless of stimulus timing and task. However, our analysis for ERPs over the frontal and fronto-central regions did not reveal any significant effects of task or laterality, or any significant interactions (ps > 0.15).

Analysis of premotor ERPs in central and centro-parietal regions revealed a significant timing × modality × task interaction (F(1,19) > 9.76, p < 0.006). Post-hoc analyses using Bonferroni’s correction for multiple comparisons showed a significant timing × task interaction for speech production (F(1,19) > 10.27, p < 0.005), but no such effect was found for hand movement (F(1,19) < 1.19, p > 0.53). Follow-up analysis for speech modality revealed that premotor ERP activities were significantly larger for temporally predictable vs. unpredictable sensory stimuli during speech cessation (t(19) > 2.95, p < 0.005) (Figure 4.4B), but no such effect was found for speech initiation (t(19) < 1.08, p > 0.28). The analysis of premotor ERPs over the parietal region yielded significant main effects of timing (F(1,19) = 10.10, p = 0.005) and laterality (F(1,19) = 37.42, p < 0.0001), as well as a significant interaction of timing × modality × laterality (F(1,19) = 8.48, p = 0.009).
Figure 4.2 Topographical distribution maps of ERP activities for initiation and cessation of speech production in 2 premotor and 10 postmotor time windows (each 50 ms long) for predictable and unpredictable conditions separately. Panels A and B display the topographical distribution maps of ERPs for initiation and cessation of speech, respectively.
Figure 4.3 Topographical distribution maps of ERP activities for hand movement initiation and cessation in 2 premotor and 10 postmotor time windows (each 50 ms long) for predictable and unpredictable conditions separately. Panels A and B display the topographical distribution maps of ERPs for hand movement initiation and cessation, respectively.
Figure 4.4 The overlaid temporal profiles of ERP activities for speech initiation and cessation during predictable (red lines) and unpredictable (black lines) conditions in a time window from −200 ms before to 500 ms after to the speech onset. The highlighted areas in each plot shows the time window in which there was a significant effect of stimulus timing. Panel A displays the profiles of ERPs and interaction plots for responses over the left fronto-central region for speech movement initiation and cessation. Panel B displays the profiles of ERPs and interaction plots for responses over the left centro-parietal region for speech movement initiation and cessation.

Post-hoc analyses using Bonferroni’s correction revealed that premotor ERP activities were significantly larger in response to temporally unpredictable vs. predictable stimuli over the left parietal area for hand movement ($F_{(1,19)} = 8.26, p = 0.01$) (Figure 4.5B), but no such effect was found for responses during speech ($F_{(1,19)} = 0.48, p = 0.49$).

The analysis of postmotor ERP activities (time windows: 0 to 500 ms) showed that hand movement elicited significantly larger neural responses compared to speech production regardless of task and stimulus timing over the frontal, fronto-central, centro-parietal, and parietal regions ($F_{(1,19)} > 6.81, p < 0.01$). Moreover, we found that
movement cessation movement elicited significantly larger postmotor ERP activities compared to movement initiation, irrespective of stimulus timing and modality ($F_{(1,19)} > 5.57, p < 0.03$).

Figure 4.5 The overlaid temporal profiles of ERP activities for hand movement initiation and cessation during predictable (red lines) and unpredictable (black lines) conditions in a time window from −200 ms before to 500 ms after to the onset of movement. The highlighted areas in each plot shows the time window in which there was a significant effect of stimulus timing. Panel A displays the profiles of ERPs and interaction plots for responses over the left fronto-central region for hand movement initiation and cessation. Panel B displays the profiles of ERPs and interaction plots for responses over the left parietal region for hand movement initiation and cessation.

4.4.3 Correlation Analysis for Speech Production

Results of correlation analysis showed that the amplitude of premotor ERPs was negatively correlated with speech motor reaction time for temporally predictable, but not unpredictable stimuli, over the frontal ($r = -0.85, p<0.0001$), fronto-central ($r = -0.82$,
regions. In addition, we found a positive correlation between premotor ERPs over the right temporo-parietal region and motor reaction time (r = +0.93, p < 0.0001) only for predictable condition. Figure 4.6A shows the topographical distribution maps of correlation coefficients for premotor ERPs (time window: -100 to 0 ms) and reaction time in response to speech initiation. We found that the correlation coefficients for speech initiation were significantly stronger (more negative) over the frontal (z = -3.6, p = 0.002), central (z = -2.98, p = 0.0014), and centro-parietal (z = -3.41, p = 0.0003) regions for temporally predictable compared with unpredictable stimuli. For speech cessation responses to temporally predictable stimuli, we found a negative correlation between premotor ERPs and reaction times over the left parieto-occipital and parietal regions, with the strongest correlation coefficient (r = -0.65, p < 0.05) over the left parietal region (Figure 4.6B). We found that for the premotor ERPs, the correlation coefficients for speech cessation were significantly stronger (more negative) for temporally predictable compared with unpredictable stimuli (z = -1.97, p = 0.02). Moreover, a positive (but not significant) pattern of correlation was observed for premotor ERPs over the central and centro-parietal regions. The temporal profiles of correlation coefficients for speech initiation and cessation at time windows from -100 to 300 ms in response to temporally predictable and unpredictable stimuli are shown in figures 4.7A and 4.7B, respectively.

4.4.4 Correlation Analysis for Hand Movement

Results of correlation analysis showed that the amplitude of premotor ERPs was negatively correlated with hand motor reaction time for temporally predictable, but not unpredictable stimuli, over the left fronto-central (r = -0.63, p = 0.003), right central (r = -
0.59, \( p=0.007 \), and right centro-parietal (\( r = -0.58, p = 0.008 \)) regions. Figure 4.6C shows the topographical distribution maps of correlation coefficients for premotor ERPs (time window: -100 to 0 ms) and reaction time in response to hand movement initiation. In addition, we found that correlation coefficients for premotor ERP responses to hand initiation were significantly stronger for predictable vs. unpredictable stimuli over the right fronto-central (\( z=-2.37, p = 0.014 \)) and left centro-parietal (\( z=-2.18, p = 0.008 \)) regions. The temporal profiles of correlation coefficients for hand movement initiation and cessation at time windows from -100 to 300 ms in response to temporally predictable and unpredictable stimuli are shown in figures 4.7C and 4.7D, respectively. For hand movement cessation, the topographical distribution maps of correlation coefficients showed a negative correlations in response to temporally predictable stimuli over the left frontal and fronto-central regions (see Figure 4.6D), with the strongest negative correlation coefficient for premotor ERP responses over the fronto-central region (\( r = -0.63, p = 0.003 \)). In addition, a positive (but non-significant) correlation pattern was observed over the left parieto-occipital for premotor ERPs. We found that the correlation coefficients for hand cessation were significantly stronger (more negative) over the left fronto-central region for premotor ERPs in response to predictable compared with unpredictable stimuli (\( z = -2.45, p = 0.007 \)).

4.5 Discussion

In the present study, we conducted a systematic investigation of the neural mechanisms of motor timing processing for initiation and cessation of speech and hand movement.
We designed a novel experimental protocol to measure motor reaction times in conjunction with ERPs when subjects were cued to start speech or hand movement and stop their ongoing movement in response to temporally predictable and unpredictable sensory stimuli. Results of our analysis revealed that motor reaction times were significantly reduced, and subjects initiated and inhibited their movement faster in response to temporally predictable compared with unpredictable stimuli in both speech and hand modalities. This finding was in line with our hypothesis and corroborated the notion that a temporal predictive mechanism may be involved in extracting timing information to facilitate motor responses to sensory stimuli that follow an established temporally regular pattern. In addition, analysis of ERP activities revealed premotor and post-motor neural activity components that were elicited in response to movement initiation and cessation visual cues during speech production and hand movement. We found that premotor ERP activities were elicited at least -100 ms prior to the onset of movement initiation and cessation and were modulated by stimulus timing (predictable vs. unpredictable) for both speech and hand motor systems.
Moreover, these premotor ERP activities were modulated by task (initiation vs. cessation) only during speech production. However, this task-specific modulation of premotor neural activities did not translate into modulation of the behavioral measures of motor reaction time. The premotor ERPs were predominantly attenuated in response to temporally predictable compared with unpredictable stimuli during speech initiation and
hand initiation and cessation responses. However, during speech cessation, an opposite pattern was observed, and the premotor ERPs were attenuated in response to unpredictable compared with predictable sensory stimuli. We also found that the amplitude of premotor ERP was significantly modulated during speech movement initiation vs. cessation, suggesting functional dissociation between neural mechanisms that drive or suppress speech production. However, no such an effect was observed during hand movement. Moreover, we observed that the premotor ERPs were correlated with behavioral measures of motor reaction time during speech and hand movement initiation and cessation, with stronger correlation associated with temporally predictable compared with unpredictable sensory stimuli. These findings supported our hypothesis and suggested that the premotor ERPs may be as robust neurophysiological biomarkers of predictive motor timing processing for movement initiation and cessation in speech and hand modalities. In the following sections, we have provided a detailed discussion of our findings to provide a unified framework for understanding the underlying neural mechanisms of temporal information processing during speech production and hand movement.

Our findings indicated that motor reaction times were significantly reduced, and movements were initiated and inhibited faster in response to predictable stimuli in both speech and hand modalities. These findings are consistent with data from previous studies that investigated movement initiation (Bevan et al., 1965; Vallesi, McIntosh, Shallice, et al., 2009) and cessation (Berchicci et al., 2015) mechanisms, and may indicate functional dissociation between the temporal processing mechanisms in the motor system in response to temporally predictable and unpredictable sensory stimuli. In
the context of a predictive coding model (Wolpert & Flanagan, 2001; Wolpert & Miall, 1996), neural representations of external stimuli are canceled out by an internally established predictive code that more closely matches the pattern of temporally predictable sensory stimuli as compared to those with unpredictable timing intervals. As supported by previous studies (Witney et al., 1999; Wolpert, 1997; Wolpert et al., 2011; Wolpert & Flanagan, 2001), we propose that the internal predictive coding mechanisms can learn, reinforce and simulate temporal regularities to facilitate motor responses to behaviorally relevant aspects of sensory stimuli (Ma & Trombly, 2004).

We found that the effect of stimulus timing was predominantly reflected in the modulation of premotor ERP activities that were elicited prior to movement initiation or cessation, and this temporal-specific modulation pattern was more consistent in the hand motor modality. For hand movement initiation and cessation, premotor ERPs emerged as a positive-polarity potential with a left-lateralized centroparietal distribution, which were attenuated in response to predictable compared with unpredictable sensory stimuli. For speech movement initiation, ERPs emerged as bilateral negative-polarity potentials over the centroparietal electrodes, which similar to hand movement, were attenuated in response to predictable compared with unpredictable sensory stimuli. In contrast, speech cessation elicited a different pattern of premotor neural activity that emerged as a bilateral positive-polarity ERP component over the centroparietal electrodes with stronger activities for predictable compared with unpredictable. The difference in temporal-specific pattern of neural activity modulation for speech initiation and cessation may indicate that the motor system utilizes distinctive neural processing mechanisms to process timing information for execution and termination of more complex movements.
such as speech production. However, a potential limitation of the implemented experimental paradigm in this study was that movement cessation responses to stop signals were followed by their initiation after the onset of go cues within the speech and hand motor modalities. Although modality within predictable and unpredictable blocks were randomized to minimize the effect associated with movement task orders (initiation vs. cessation), it should be noted that one should be cautious to draw strong conclusions related to the observed differences between movement initiation and cessation effects.

The observed neural activities over the centroparietal electrodes in the present study may be the neural signature of a temporal predictive coding mechanism that incorporates the timing aspects of sensory stimuli and translates them into motor actions. Previous studies have proposed that the parietal cortex plays an important role in estimation and motor replication of temporal intervals (Bueti, Walsh, Frith, & Rees, 2008), suggesting that this brain region may be the neural interface that translates temporal information into motor commands. In the present study, we demonstrated that premotor ERPs over the centroparietal electrodes were suppressed and movements were performed with shorter reaction times for predictable stimuli, indicating that the translation of timing information into motor responses was more accurate and robust when temporal information were predictable in nature. Based on these results, we propose that extracting timing information and translating this into motor commands is a key function of movement planning and execution mechanisms and is a critical element of a temporal predictive coding mechanism in the motor system that drives or suppresses motor actions with extremely high temporal precision.
The notion of the internal predictive model has been corroborated by findings of previous studies showing that auditory neural responses to tones triggered by button press (Chen et al., 2012; Mifsud et al., 2016; Timm et al., 2016) or self-produced speech (Aliu et al., 2009; Behroozmand & Larson, 2011; Behroozmand et al., 2011; Behroozmand et al., 2016; Chang et al., 2013; Heinks-Maldonado et al., 2005; Ventura et al., 2009) were suppressed compared with when subjects passively listened to the playback of the same self-generated sounds. This motor-induced suppression effect has been suggested to reflect decreased contribution of the sensory feedback mechanisms for sensorimotor processing of self-generated stimuli. In addition, temporal predictability of sensory stimuli has also been suggested to enhance internal predictive coding mechanisms. Supporting evidence for this notion has been provided by studies showing that motor-induced suppression of auditory cortex has been increased for stimuli with predictable (fixed) compared with unpredictable (variable) temporal dynamics (Behroozmand et al., 2011; Behroozmand et al., 2016; Chen et al., 2012). Moreover, behavioral studies have demonstrated that movement reaction times were significantly decreased in response to temporally predictable compared with unpredictable sensory stimuli (Bevan et al., 1965; Niemi & Naatanen, 1981; Vallesi, McIntosh, Shallice, et al., 2009).

In other studies, event-related desynchronization (ERD) of beta band (13-30 Hz) activity was reported in the subthalamic nucleus (STN) of basal ganglia (Kuhn et al., 2004) and cortical motor regions (Alegre et al., 2003) prior to the onset of hand responses to self-paced movement or movement produced in response to temporally predictable sensory stimuli. In patients with Parkinson’s disease, damages to the basal ganglia and other structures within the corticostriatal network was associated with slower attenuation
of preparatory beta-band ERD activities, which was accompanied by a deficit in temporal processing during motor planning and execution (Praamstra & Pope, 2007). These findings suggested that the corticostriatal network provides the neural substrate for a predictive coding mechanism that mediates movement planning and execution in response to temporally predictable stimuli.

Our analysis showed that correlation between the amplitude of premotor ERPs and motor reaction time was significantly stronger in response to temporally predictable compared with unpredictable stimuli. This finding indicates that the premotor ERP is a neurophysiological biomarker of motor behavior and can be used to predict reaction time during speech and hand movement initiation and cessation tasks. In addition, the ERP biomarkers reflect temporal predictive mechanisms that mediate faster movement in response to predictable sensory stimuli. Based on these findings, we suggest that stimuli with temporal regularities are more accurately encoded by the internal predictive mechanisms, and the neural representation of this effect is reflected in the premotor ERP activities, which are elicited by movement planning mechanisms in the motor system. The outcome of this process leads to motor commands that drive or suppress movements faster and with higher temporal precision during speech production and hand movement. The observed differences between correlation patterns unfolds new information about temporal information processing in the motor system and suggests that the brain may differentially process timing information to serve distinct functions for movement initiation and cessation during speech production and hand movement.
Chapter 5

Effects of Aging on Temporal Predictive Mechanisms of Speech and Hand Motor Reaction Time

5.1 Abstract

Evidence from previous studies has suggested that movement execution in younger adults is accelerated in response to temporally predictable vs. unpredictable sensory stimuli. This effect indicates that external temporal information can modulate motor behavior; however, how aging can influence temporal predictive mechanisms in the motor system has yet to be understood. The objective of the present study was to investigate aging effects on the initiation and inhibition of speech and hand movement reaction times in response to temporally predictable and unpredictable sensory stimuli. Fifteen younger (mean age: 22.6) and fifteen older (mean age: 63.8) adults performed a randomized speech vowel vocalization or button press initiation and inhibition tasks in two counterbalanced blocks in response to temporally predictable and unpredictable visual cue stimuli. Results showed that motor reaction time was accelerated in both younger and older adults for predictable vs. unpredictable stimuli during initiation and inhibition of speech and hand movement. However, older adults were significantly slower than younger adults in motor execution of speech and hand movement when stimulus timing was unpredictable. Moreover, we found that overall, motor inhibition of speech and hand was executed faster than their initiation. Our findings suggest that older adults can compensate age-related decline in motor reaction times by incorporating external temporal information and execute faster movement in response to predictable stimuli whereas unpredictable temporal information cannot counteract aging effects efficiently and lead to less accurate motor timing predictive codes for speech production and hand movement.
5.2 Introduction

Temporal information processing is a fundamentally important function of the human nervous system, which enables us to process sensory stimuli and generate motor responses with high temporal precision. Beside our nervous system’s ability to generate temporally precise and accurate movements in our limb motor system (Bertelson & Boons, 1960; Drazin, 1961; Johari & Behroozmand, 2017a, 2017b; Karlin, 1959; Klemmer, 1956), studies have shown that temporal aspects of sensory stimuli can also enhance motor timing responses during speech production (Behroozmand et al., 2016; Johari & Behroozmand, 2017a, 2017b). Converging evidence from these studies indicates that temporally predictable sensory stimuli can accelerate response time for movement initiation (Bertelson & Boons, 1960; Drazin, 1961; Johari & Behroozmand, 2017a, 2017b; Karlin, 1959; Klemmer, 1956; Vallesi, McIntosh, & Stuss, 2009) and inhibition (Berchicci et al., 2015; Johari & Behroozmand, 2017b; Li, Krystal, & Mathalon, 2005) compared to unpredictable stimuli. It has been suggested that the motor system itself can extract temporal information from sensory stimuli (Wolpert, 1997; Wolpert & Flanagan, 2001) and thus facilitate temporal processing of movement initiation and inhibition response time during speech production (Behroozmand et al., 2016; Johari & Behroozmand, 2017a, 2017b) and hand movement (Bertelson & Boons, 1960; Bevan et al., 1965; Johari & Behroozmand, 2017a, 2017b; Karlin, 1959; Vallesi, McIntosh, Shallice, et al., 2009).

However, studies regarding temporal mechanisms in the motor system have focused primarily on younger adults (Berchicci et al., 2015; Bevan et al., 1965; Coull et al., 2016; Johari & Behroozmand, 2017a, 2017b; Klemmer, 1956; Koppe et al., 2014; Li
et al., 2005; Ramautar, Kok, & Ridderinkhof, 2004; Vallesi, McIntosh, Shallice, et al., 2009; Vallesi, McIntosh, & Stuss, 2009) and it remains elusive how aging can affect temporal aspects of movement initiation and inhibition in response to temporally predictable and unpredictable sensory stimuli.

The aim of the present study is to examine how aging can affect motor response reaction time for initiation and inhibition of speech and hand movement when sensory stimulus timing is predictable or unpredictable. In what follows, we will provide a general overview of how temporal aspects of sensory stimuli can modulate movement initiation and inhibition of speech and hand movement in younger adults and will review the findings of studies that examined aging effects on the mechanisms of movement reaction time. We will finally conclude with discussing our novel approach to address questions on how temporal aspects of sensory stimuli can modulate speech and hand motor behavior in older adults and what predictions were established in the present study.

5.2.1 Temporal Aspects of Movement Initiation and Inhibition

The temporal processing of movement has been examined using motor reaction time tasks during which subjects were required to press a button (Bertelson & Boons, 1960; Bevan et al., 1965; Coull et al., 2016; Johari & Behroozmand, 2017a, 2017b; Karlin, 1959; Klemmer, 1956; Koppe et al., 2014; Vallesi, McIntosh, Shallice, et al., 2009) or produce a speech sound (Behroozmand et al., 2016; Johari & Behroozmand, 2017a, 2017b). Reaction time has been considered as a behavioral index of information processing (Pachella, 1973) and has been used to address how temporal information can modulate movement response times (Drazin, 1961; Johari & Behroozmand, 2017a,
Some studies have manipulated inter-stimulus intervals (ISI) to examine temporal mechanisms in the motor system (Koppe et al., 2014; Mattes & Ulrich, 1997; Thickbroom et al., 2000). These studies have revealed that fixed ISIs can accelerate hand movement initiation compared with variable ISIs, suggesting that the motor system is able to use past timing information to establish temporal predictions in response preparation for future movement. Other studies have used the well-established Foreperiod (FP) paradigm to examine temporal mechanisms in the motor system (Bevan et al., 1965; Karlin, 1959; Klemmer, 1956; Li et al., 2005; Vallesi, McIntosh, Shallice, et al., 2009). The FP task involves a warning signal that appears on the screen, followed by an interval before the imperative signal with predictable (fixed) or unpredictable (variable) timing (Karlin, 1959). From an information processing perspective, FP provides a mechanism for temporal preparation for the upcoming imperative signal. Studies demonstrated that during short FPs, a predictable interval between warning and imperative signals can accelerate hand movement initiation response times compared to unpredictable FPs (Niemi & Naatanen, 1981; Vallesi, McIntosh, Shallice, et al., 2009). The faster reaction time for fixed FPs indicates that temporally predictable information can enhance the preparatory phase of movement initiation compared to unpredictable intervals.

In contrast to movement initiation, few studies have examined the effect of temporal aspects of sensory stimuli on movement inhibition reaction time (Berchicci et al., 2015; Johari & Behroozmand, 2017b; Li et al., 2005). While some studies have found that movement inhibition is not sensitive to the predictability of sensory stimuli (Logan &
Burkell, 1986; Ramautar et al., 2004), others indicated that temporally predictable sensory stimuli can accelerate movement inhibition compared to unpredictable stimuli (Berchicci et al., 2015; Johari & Behroozmand, 2017b; Li et al., 2005). Nevertheless, it is relatively unclear whether temporal processing of movement initiation and inhibition share common mechanisms. A recent study showed that movement initiation reaction time was positively correlated with movement inhibition reaction time in response to both temporally predictable and unpredictable sensory stimuli (Johari & Behroozmand, 2017b), and the correlation was stronger when timing information was predictable. These findings suggest that even though movement initiation and inhibition may be driven by distinct functional mechanisms in the brain, they may share common mechanisms for temporal information processing.

5.2.2 Effects of Temporal Predictability on Speech and Hand Movement Reaction Time

Temporal aspects of sensory stimuli can modulate response time for both speech production and hand movement, but it is still unclear if these modalities share common temporal mechanisms. Previous studies have demonstrated interaction between speech production and hand movement at both neural (Binkofski, Buccino, Posse, et al., 1999; Binkofski, Buccino, Stephan, et al., 1999; Corballis, 2003; Gentilucci et al., 2009; Gentilucci & Volta, 2008) and behavioral levels (Johari & Behroozmand, 2017b). Although most studies on temporal aspects of movement initiation and inhibition have focused on hand movement (Berchicci et al., 2015; Bertelson & Boons, 1960; Coull et al., 2016; Koppe et al., 2014; Li et al., 2005; Mattes & Ulrich, 1997; Vallesi, McIntosh,
Shallice, et al., 2009; Vallesi, McIntosh, & Stuss, 2009), a few studies have examined these mechanisms during speech production (Behroozmand et al., 2016; Johari & Behroozmand, 2017a, 2017b). Similar to effects observed during hand movements, faster reaction times were registered in response to temporally predictable vs. unpredictable sensory stimuli during speech initiation (Johari & Behroozmand, 2017a, 2017b) and inhibition (Johari & Behroozmand, 2017b). Moreover, motor reaction times for initiation and inhibition of hand movement were positively correlated with speech initiation and inhibition, suggesting that speech production and hand movements share common temporal mechanisms to initiate or inhibit movement in response to temporally predictable and unpredictable sensory stimuli.

5.2.3 The Temporal Predictive Code in The Motor System

We recently proposed that temporal aspects of movement initiation and inhibition follow the principle of the predictive code model (Johari & Behroozmand, 2017a, 2017b). According to this model, the brain can extract temporal aspects of sensory stimuli to establish predictions about the timing of upcoming imperative signals, and these predictions are more robust and precise when temporal information is predictable. Specifically, we suggested that motor system may recruit distinct functional mechanisms to initiate/inhibit movement in response to temporally predictable vs. unpredictable sensory stimuli (Johari & Behroozmand, 2017b). The notion of a temporal predictive code in motor system is supported by findings in a recent study showing that different cortical regions of the brain within the parietal lobe are involved in processing temporally predictable vs. unpredictable intervals (Coull et al., 2016). This latter study suggested that for temporally predictable intervals, the brain can extract temporal information from
sensory stimuli and establish temporal expectancy about the timing of upcoming
imperative signals. Temporally unpredictable intervals, however, are supported by the
hazard function in which the probability of the upcoming imperative signal increases as
time elapses, leading to slower and less precise motor responses.

5.2.4 Aging Effects on Temporal Aspects of Movement Production

Temporal predictive coding mechanisms in the motor system are mainly studied
in younger adults (Behroozmand et al., 2016; Bertelson & Boons, 1960; Karlin, 1959;
Koppe et al., 2014; Mattes & Ulrich, 1997; Vallesi, McIntosh, Shallice, et al., 2009), and
the effect of aging on these mechanisms has remained relatively unclear. Studies have
found that as individuals age, they show increasing difficulties in processing of temporal
information at sensory (Balci, Meck, Moore, & Brunner, 2009; Craik & Hay, 1999) and
motor levels (Fozard, Vercruyssen, Reynolds, Hancock, & Quilter, 1994; Levin,
Fujiyama, Boisgontier, Swinnen, & Summers, 2014; Munoz, Broughton, Goldring, &
Armstrong, 1998). Older adults are slower than younger adults during motor reaction
time tasks (Singleton, 1955; Vallesi, McIntosh, & Stuss, 2009). This slower reaction time
in older adults may be attributed to a slower central processing, which can subsequently
decelerate movement production reaction time (H. Yan Jerry R. Thomas George E.
Stelmach, 1998). Alternatively, this effect can also be accounted for by a specific
abnormality in temporal information processing in older adults (Block, Zakay, &
Hancock, 1998; Craik & Hay, 1999; Espinosa-Fernández, Miró, Cano, & Buela-Casal,
2003; Zanto et al., 2011). Older adults have also been reported to make more errors than
younger adults during the performance of time perception-related tasks (Espinosa-
Fernández et al., 2003). Specifically, older adults are shown to overestimate temporal
intervals suggesting their difficulty in processing temporal information for sensory stimuli (Block et al., 1998). It has been suggested that motor timing and time perception are subserved by common neural networks in motor cortex (Schubotz, Friederici, & Von Cramon, 2000), so that slower reaction times in older adults might be due to a general decline in temporal processing for movement production.

While studies have shown abnormal temporal processing older individuals, it is not fully understood how aging can affect temporal predictive coding mechanisms in the motor system. It has been demonstrated that older adults are significantly slower than younger adults in hand movement initiation during both fixed and variable FPs, suggesting age-related decline in temporal predictive code mechanisms limb motor system (Vallesi, McIntosh, & Stuss, 2009). Moreover, older adults have been shown to fail to use explicit temporal cues to accelerate hand movement reaction time during short FPs, while younger subjects responded faster than older adults and used temporal cues to facilitate hand movement initiation (Zanto et al., 2011). In contrast, a recent study (Chauvin, Gillebert, Rohenkohl, Humphreys, & Nobre, 2016) has found that both older and younger adults can benefit from explicit temporal cues during short FPs to accelerate hand movement reaction times. Therefore, findings on temporal predictive mechanisms in older adults do not conform to a consistent framework across different studies and it is not fully understood how aging may influence temporal processing mechanisms in the human motor system.
5.2.5 Study Objectives

Although previous studies have provided some insights into age-related changes of temporal processing mechanisms during movement production (Chauvin et al., 2016; Vallesi, McIntosh, & Stuss, 2009; Zanto et al., 2011), our understanding of how aging can influence these mechanisms has been limited by two factors. First, previous studies on the effects of aging on temporal aspects of movement production have been limited to comparing older and younger adults only during hand movement (Chauvin et al., 2016; Vallesi, McIntosh, & Stuss, 2009; Zanto et al., 2011). Therefore, it is still unclear whether temporal aspects of speech production are similarly or differently affected by aging. Second, the effect of aging on temporal aspects of movement production has been studied during hand movement initiation (Chauvin et al., 2016; Vallesi, McIntosh, & Stuss, 2009; Zanto et al., 2011), and less is known about aging effects on these mechanisms during movement inhibition for speech production and hand movement.

The present study was motivated by the question of how aging would influence the temporal predictive coding mechanisms in the motor system during initiation and inhibition of speech production and movement. We designed an experiment in which both younger and older adults performed a randomized speech (vowel vocalization) or hand (button press) motor response reaction time task in two counterbalanced blocks with temporally predictable and unpredictable visual stimuli. The visual stimuli were presented to cue the subjects to first initiate and then inhibit the ongoing motor action during speech or hand movement tasks, with either fixed or randomized time intervals during predictable and unpredictable blocks, respectively. We used motor response reaction time as a behavioral index of temporal information processing during speech
production and hand movement. This novel experimental design provided a unified framework to simultaneously examine the effects of temporal predictability on initiation and inhibition of speech production and hand movement in both younger and older adults, and to examine aging effects on these temporal information processing mechanisms. We hypothesized that the motor reaction time would be slower in older compared with younger adults in both speech production and hand movement modalities. However, due to the absence of empirical evidence on the effects temporal predictability, and initiation vs. inhibition motor tasks, we took an exploratory approach to determine the effects of these factors in our data analyses.

5.3 Methods and Materials

5.3.1 Subjects

A total of 15 young (7 males and 8 females, age range 20-30 years old, mean: 22.6) and 15 older subjects (8 males and 7 females, age range 50-73 years old, mean: 63.8) participated in this study. Subjects reported no history of psychiatric or neurological conditions, and they had no history of speech or hearing impairment. All subjects also had normal or corrected vision. Handedness of subjects was obtained using the Edinburgh handedness inventory; and all were right handed (score range 72-100). All study procedures, including recruitment, data acquisition, and informed consent were approved by the University of South Carolina Institutional Review Board, and subjects were monetarily compensated for their participation.
5.3.2 Experimental Design

The experiment was conducted in a sound attenuated booth in which subjects performed the experimental tasks. The experiment consisted of two random-order tasks that involved initiation and inhibition of speech and hand movement. Subjects were instructed to prepare to perform one of the above motor tasks (speech or hand) following the onset of a relevant visual cue on the screen (see figure 2.1 in chapter 2). During each task, subjects were instructed to prepare for the cued movement and start pressing a button or vocalizing a steady vowel sound /a/ after a circle (go signal) appeared on the screen and stop after the circle disappeared (see figure 2.1 in chapter 2). Subjects were seated in a comfortable chair directly in front of the computer screen at a distance of about 15-20 inches to easily see the presented visual cues. The background of the screen was black and the visual cues appeared as white circles 1.5 inches in diameter. We designed two counterbalanced blocks within which subjects performed the speech and hand movement tasks in a randomized order: 1) temporally-predictable block, in which there was a fixed time interval of 1500 ms between the onset of the Visual Cue and Go signal, as well as the Go and Stop signals, and 2) temporally-unpredictable block in which the time interval between the Visual Cue and Go signal, as well as the Go and Stop signals, was randomized between 1000-2000 ms. During each block, a total number of 220 trials were collected, with approximately 110 trials for speech and hand movement initiation and inhibition. The inter-trial-interval (ITI) was 2-3 seconds in each block and subjects took a 5-minute break between the two blocks. All the experimental parameters, including Visual Cues, Go, and Stop signals and the time intervals between them were controlled by a custom-made program implemented in Max 5.0 (Cycling '74, San
Francisco, CA). Additionally, timing within trials (T) and order of trials (speech and hand) were controlled by the Max program. Subjects’ responses including vowel sound vocalizations and button presses were recorded on a laboratory computer for the analysis of the reaction time. The speech signal was recorded through a head-mounted AKG condenser microphone (model C520) amplified by a Motu Ultralite-MK3 module.

5.3.3 Reaction Time Analysis

For each subject, measures of reaction time were obtained for both predictable and unpredictable blocks (button press initiation and inhibition, speech initiation and inhibition). The reaction time for each condition was extracted using a custom-made MATLAB code by calculating the time difference between the onset of the go and stop visual cues and the initiation and inhibition of speech and hand movements, respectively. A repeated measure ANOVA was performed to examine effects of group (younger vs. older adults), timing (predictable vs. unpredictable), modality (Speech vs. hand) and task (initiation vs. inhibition) as well as their interaction on reaction time measures. The alpha level was 0.05 and post-hoc tests were corrected using Bonferroni correction for multiple comparisons.

5.4 Results

The results of the ANOVA yielded significant main effects of group (F(1,28) = 5.16, p = 0.03, η² = 0.15), timing (F(1,28) = 24.78, p < 0.0001, η² = 0.47) and task (F(1,28) = 87.31, p < 0.0001, η² = 0.74) on the measure of motor reaction time. The timing and group effects showed two-way interactions (F(1,28) = 6.75, p = 0.01, η² = 0.20), and post hoc analysis revealed that younger adults were significantly faster than older adults.
during the unpredictable \((t_{118} = 3.54, p = 0.001)\) but not the predictable condition \((t_{118} = 0.89, p = 0.42)\) (see figure 5.1A). Moreover, the task effect showed two-way interactions with modality and task \((F_{1,28} = 8.19, p = 0.008, \eta^2 = 0.22)\), indicating that hand initiation \((t_{118} = 3.22, p = 0.002)\), but not inhibition \((t_{118} = 0.26, p = 0.79)\), was significantly faster than speech initiation regardless of timing and group factors (see figure 5.1B).

Table 5.1 Shows the mean reaction time and standard deviation (SD) for younger and older adults during initiation and inhibition of speech production and hand movement for both predictable and unpredictable stimulus timing conditions.

<table>
<thead>
<tr>
<th></th>
<th>Predictable</th>
<th>Unpredictable</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initiation</td>
<td>Inhibition</td>
<td>Initiation</td>
<td>Inhibition</td>
<td>Initiation</td>
<td>Inhibition</td>
<td>Initiation</td>
<td>Inhibition</td>
<td>Initiation</td>
<td>Inhibition</td>
<td>Initiation</td>
<td>Inhibition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger</td>
<td>Speech</td>
<td>436 ± 49</td>
<td>444 ± 68</td>
<td>340 ± 74</td>
<td>307 ± 38</td>
<td>460 ± 73</td>
<td>565 ± 165</td>
<td>380 ± 52</td>
<td>421 ± 155</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hand</td>
<td>377 ± 79</td>
<td>403 ± 54</td>
<td>304 ± 64</td>
<td>353 ± 54</td>
<td>401 ± 47</td>
<td>489 ± 145</td>
<td>347 ± 38</td>
<td>478 ± 145</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5.1 A) The group (old vs. young) by timing (predictable vs. unpredictable) interaction for the mean reaction time, indicating that older adults were slower than younger adults when stimulus timing was unpredictable. B) Task (initiation vs. inhibition) by modality (speech vs. hand) interaction, indicating that movement initiation for speech was slower than hand irrespective of stimulus timing. In each panel, error bars show the standard error of the mean (SEM) for each experimental factor, separately.
As mentioned above, the significant group by timing interaction indicated that the older adults were slower than the younger only when sensory stimuli were temporally unpredictable regardless of the response modality and task. Therefore, we probed the association between the age and motor temporal processing by using age as a scale variable. Given that there was no significant age by task or age by modality interactions in repeated-measures ANOVAs, the measures of motor reaction time were combined as a dependent variable across both tasks (initiation and inhibition) and response modalities (speech and hand), and age and stimulus timing were included as independent variables of interest in our regression analysis. Results of this analysis yielded a significant timing by age interaction (beta = 0.58, \( p = 0.009 \)). Then, we ran follow up correlation analyses between the measures of reaction time and age for the predictable and unpredictable conditions, separately. The correlations were corrected for multiple comparisons using Bonferroni’s method. The results confirmed that age was positively correlated with reaction time for the unpredictable (\( r_{(118)} = 0.33, p < 0.0001 \)), but not the predictable (\( r_{(118)} = 0.09, p = 0.37 \)) stimulus timing condition (Figure 5.2). The correlation between age and reaction time was significant even after the task and modality factors were partialed out for both unpredictable (\( r_{(116)} = 0.34, p < 0.0001 \)) and predictable (\( r_{(116)} = 0.10, p = 0.28 \)) conditions. Finally, Levene's test was preformed to examine whether the significant correlation for unpredictable condition was because of inequality of variances between younger and older adults’ reaction times. Results did not reveal a significant difference between variances for predictable (\( F_{(7,112)} = 1.5, p = 0.16 \)) and unpredictable (\( F_{(7,112)} = 1.8, p = 0.10 \)) conditions, indicating that significant correlation for temporally
unpredictable stimuli was not accounted for by inequality of variances between younger and older adults’ reaction times.

Figure 5.2 Correlation plots between the measures of reaction time and age overlaid across movement initiation and inhibition tasks in both speech and hand modalities. Correlations plots are demonstrated for A) temporally predictable, and B) temporally unpredictable stimuli, separately.

5.5 Discussion

The present study investigated how aging can affect motor reaction time in response to temporally predictable vs. unpredictable sensory stimuli during the initiation and inhibition of speech production and hand movement. We found that in general, motor reaction time was faster in response to temporally predictable vs. unpredictable sensory stimuli, irrespective of movement modality (speech vs. hand) and task (initiation vs. inhibition). However, our data showed that aging had a significant effect on motor response reaction time for temporally predictable vs. unpredictable sensory stimuli. While younger and older adults did not significantly differ in their responses to temporally predictable sensory stimuli, older adults were slower compared to younger
adults in response to temporally unpredictable sensory stimuli, regardless of task and response modality. In addition, movement inhibition reaction time was faster than that for initiation, and this task effect was modality-specific. Finally, we found that participants’ age was positively correlated with movement reaction time only in response to temporally unpredictable stimuli.

The finding that older and younger adults’ reaction time was not significantly different for predictable stimuli is consistent with data from a previous studies by Chauvin et al. (Chauvin et al., 2016) in which it has been shown that older adults can use temporal cues to accelerate their motor response reaction time. In contrast, data from a study by Vallesi et al. (Vallesi, McIntosh, & Stuss, 2009) showed that older adults were slower than younger adults in response to temporally predictable stimuli. This inconsistency with respect to motor responses to predictable intervals might be in part due to the timing intervals that were used in Vallesi et al.’s study (Vallesi, McIntosh, & Stuss, 2009) in which they included short and long intervals for both predictable and unpredictable blocks. We argue that using mixed length intervals for predictable stimuli may have decreased the predictability effect of sensory stimuli in Vallesi et al.’s study (Vallesi, McIntosh, & Stuss, 2009), which was systematically different from the fixed intervals used in the present study.

Our results have suggested that the motor mechanisms of the temporal predictive code are relatively spared for initiation and inhibition of speech and hand movements when stimulus timing is predictable. However, we found that movement production was significantly slower in older compared with younger adults specifically in response to temporally unpredictable sensory stimuli. In addition, the significant correlation between
individuals’ age and their motor reaction time in response to unpredictable stimuli confirms that movement reaction times for sensory stimuli with unpredictable timing increases as people age. This correlation, along with slower reaction times for older adults during unpredictable timing, provides new insights into temporally specific age-related deficits in movement production mechanisms for initiation and inhibition of speech and hand motor responses.

The older adults’ slower motor reaction times for temporally unpredictable stimuli may be discussed in the context of temporal expectancy and the hazard function (Coull et al., 2016). It has been suggested that the brain uses a hazard function to process temporally unpredictable intervals, whereas temporal expectancy supports the processing of predictable intervals (Coull et al., 2016). Based on our findings, we suggest that aging is associated with decline of the hazard function, which can consequently lead to less precise estimates about the timing of upcoming imperative signals for movement initiation and inhibition during unpredictable timing. In contrast, temporal expectancy mechanisms are preserved for movement production in aging, suggesting that similar to younger adults, older subjects can use temporally predictable information to establish expectancy about the timing of an upcoming imperative signal and accelerate their motor response reaction time.

The finding that younger adults were faster than older adults in response to temporally unpredictable speech stimuli may reflect age-related changes in processing of complex sensory-motor stimuli. Older adults may experience increased difficulties in processing temporal information during a complex and more cognitively demanding sensory-motor task compared with younger adults, partially due to their limitation in
allocation of neural resources during information processing for stimuli with
unpredictable temporal patterns (Jordan & Rabbitt, 1977; Ma & Trombly, 2004). In this
study, we used a fixed timing for temporally predictable stimuli during the motor reaction
time task and this enabled subjects to establish a stronger temporal expectancy about the
timing of the upcoming imperative signal. In contrast, timing variability in the
unpredictable condition may have resulted in an increase in the level of complexity for
temporal information processing, leading to diminished cognitive and sensorimotor
performance in older adults compared with their younger counterparts.

We also found that hand movement initiation was faster than speech initiation
regardless of timing and aging group. This supports our previous findings that in general,
hand movement is executed with faster motor reaction time compared with that during
speech production (Johari & Behroozmand, 2017a, 2017b). We suggest that this effect is
accounted for by the difference in complexity of the executed motor task in speech vs.
hand modality (Gajewski & Falkenstein, 2013). Our data suggest that due to the inherent
complexity of speech production compared with hand movement, speech initiation
requires activation and coordination of a large group of muscles (e.g. respiration, larynx,
and articulation) at different levels of the speech subsystem compared to a less complex
motor task for hand movement during button press (Johari & Behroozmand, 2017b).

5.6 Conclusion

In summary, our findings revealed that temporal predictive mechanisms in the
motor system are more prominently affected by aging in response to sensory stimuli that
follow a temporally unpredictable vs. predictable pattern. However, we found that for
temporally predictable stimuli, movement production mechanisms are relatively spared in older adults compared with their younger counterparts. These findings provide new insights into the effects of aging on the temporal aspects of information processing for movement production. Future studies are warranted to promote our understanding of other possible age-related effects on the underlying mechanisms involved in temporal information processing for speech production and hand movement.
Chapter 6

Behavioral and Neural Correlates of Normal Aging Effects on Motor Preparatory Mechanisms of Speech Production and Limb Movement

---

6.1 Abstract

Normal aging is associated with decline of the sensorimotor mechanisms that support movement function in the human brain. In this study, we used behavioral and event-related potential (ERP) recordings to investigate the effects of normal aging on the motor preparatory mechanisms of speech production and limb movement. The experiment involved two groups of older and younger adults who performed randomized speech vowel vocalization and button press motor reaction time tasks in response to temporally predictable and unpredictable visual stimuli. Behavioral results revealed age-related slowness of motor reaction time only during speech production in response to temporally unpredictable stimuli, and this effect was accompanied by increased pre-motor ERP activities in older vs. younger adults during the speech task. These results indicate that motor preparatory mechanisms of limb movement during button press are not affected by normal aging, whereas the functional capacity of these mechanisms is reduced in older adults during speech production in response to unpredictable sensory stimuli. These findings suggest that the aging brain selectively compromises the motor timing of speech and recruits additional neural resources for motor planning and execution of speech, as indexed by the increased pre-motor ERP activations in response to temporally unpredictable vs. predictable sensory stimuli.

6.2 Introduction

In humans and many animal species, the central nervous system has developed highly specialized mechanisms to generate precisely timed and fine-tuned movements for interaction with the environment and reaching the goals of a wide range of behaviorally relevant tasks. Although the underlying neural mechanisms of movement timing
processing are not fully understood, recent theories have proposed that the brain can learn and simulate the temporal patterns of sensory stimuli and establish an internal model to predict the neural representations of motor timing and their expected sensory feedback (Wolpert, 1997; Wolpert & Flanagan, 2001). This mechanism forms the basis of skilled motor behavior through establishing an internal temporal predictive code for estimating the next state of movements and their upcoming sensory consequences even before the actual sensory feedback has become available. This enhanced functional capacity plays a key role in optimized motor behavior with relevance to timing of current and upcoming sensory stimuli. However, an important question remains as to how normal aging affects the neural and behavioral mechanisms of motor timing processing and control.

Findings of previous studies in young adults have shown that the internal predictive mechanisms are modulated by the inherent temporal characteristics of external sensory stimuli (Behroozmand et al., 2016; Berchicci et al., 2015; Bertelson & Boons, 1960; Bevan et al., 1965; Koppe et al., 2014; Vallesi, McIntosh, Shallice, et al., 2009). This effect has been suggested to account for increased accuracy of the temporal predictive codes in response to predictable vs. unpredictable sensory stimuli, and subsequently faster motor reaction times in response to stimuli with predictable timing patterns (Johari & Behroozmand, 2017a, 2017b; Karlin, 1959; Klemmer, 1956; Koppe et al., 2014; Li et al., 2005).

The underlying neural mechanisms of internal predictive codes have been investigated using neurophysiological recordings from the visual (Samaha, Bauer, Cimaroli, & Postle, 2015), auditory (Lange, 2009), and somatosensory (Haegens, Luther, & Jensen, 2012; van Ede, de Lange, Jensen, & Maris, 2011; van Ede, Szebényi, & Maris,
2014) systems. Findings of these studies have highlighted the role of the alpha and beta band neural oscillations in generating internal predictive codes and suggested that the timing of external stimuli can enhance such top-down predictive mechanisms and subsequently facilitate neural processing of incoming sensory information.

An important proposal of the internal forward model theory (Wolpert, 1997; Wolpert & Flanagan, 2001) is that temporal information processing is not only mediated by anticipatory mechanisms in the sensory system, but that this process utilizes predictive coding mechanisms in the motor system that can further enhance temporal information processing during movement production. This notion has been supported by previous studies on limb movement (Bard et al., 1992; Blakemore et al., 1998; Johansson & Westling, 1988; Witney et al., 1999) and speech production (Behroozmand et al., 2011; Behroozmand et al., 2016; Chen et al., 2012; Kotz & Schmidt-Kassow, 2015), demonstrating that when sensory stimuli arise from self-produced motor actions, the internal forward model predicts the temporal relationships between motor commands and their sensory consequences. Findings of these studies have indicated that temporally predictable patterns can be learned by the internal forward model to modulate perceptual sensations arising from self-generated motor actions. During limb movement, the modulation of perceptual sensations has been shown to be reflected in attenuation of sensory responses to self-produced motor responses (Blakemore et al., 2000; Blakemore et al., 1998), which is hypothesized to be caused by central cancellation of sensory responses by the efference copies of the motor commands. In addition, studies have shown that the neural correlates of limb motor movement are differentially modulated by predictable vs. unpredictable stimuli (Alegre et al., 2003; Koppe et al., 2014; Schwartz...
et al., 2012), indicating that the internal predictive mechanisms are affected by temporal
dynamics of incoming sensory stimuli. In the speech modality, studies have also
demonstrated that neural responses to alterations in speech auditory feedback are
differentially modulated in response to temporally predictable vs. unpredictable sensory
stimuli, with greater motor-induced suppression in response to predictable feedback
alteration stimuli (Behroozmand et al., 2016; Chen et al., 2012).

Single neuron recordings in primates have further corroborated the notion of an
internal predictive mechanism during vocal production and motor control by showing
that neurons in the primates’ auditory cortex were suppressed prior to the onset of self-
produced vocalizations (Eliades & Wang, 2003). This effect was suggested to reflect top-
down predictive mechanisms (i.e. efference copies) that fine-tune sensory neural
representations through motor-induced suppression of cortical auditory neurons before
the onset of self-produced vocalizations. Further insights into the neural bases of
temporal predictive mechanisms have been provided by recent neuroimaging studies in
humans showing increased activation of a network involving the supplementary motor
area (SMA) (Thickbroom et al., 2000), right dorsolateral (DLFPC) and ventrolateral
(VLPFC) prefrontal cortex (Vallesi, McIntosh, Shallice, et al., 2009; Vallesi et al., 2007),
and the left inferior parietal cortex (IPC) (Coull et al., 2016) during movement initiation
in response to temporally unpredictable vs. predictable stimuli. These findings support
the key role of a frontoparietal network in differential neural processing of motor timing
in response to predictable vs. unpredictable sensory stimuli. This latter notion was further
supported by event-related potential (ERP) recordings revealing distinct patterns of
neural activities during speech and limb motor responses to temporally predictable vs.
unpredictable stimuli in young healthy adults (Alegre et al., 2003; Berchicci et al., 2015; Johari & Behroozmand, 2017a, 2018). Findings of these studies suggest that pre-motor ERPs serve as a biomarker of temporal predictive coding during the planning phase of movement by showing that these neural activities were significantly suppressed in response to predictable vs. unpredictable stimuli, and that this suppression was correlated with faster motor reaction times in response to temporally predictable sensory stimuli (Johari & Behroozmand, 2017a, 2018).

Despite the existing evidence supporting the notion of temporal predictive mechanisms during movement production, our understanding about the effect of normal aging on these mechanisms has remained limited. Normal aging is associated with functional decline in the temporal processing mechanisms of movement production, as indexed by age-related slowness of motor reaction time in response to externally presented sensory stimuli (Balci et al., 2009; Bherer & Belleville, 2004; Diersch, Jones, & Cross, 2016; Seidler et al., 2010; Sterr & Dean, 2008). Such reduced capacity for motor timing processing has been suggested to result from declined internal temporal predictive mechanisms in older adults (Vieweg, Stangl, Howard, & Wolbers, 2015), and their reduced accuracy in predicting the timing of movement sequences during action occlusion tasks (Diersch, Cross, Stadler, Schütz-Bosbach, & Rieger, 2012; Diersch et al., 2013; Wolpe et al., 2016).

The age-related decline in the neural mechanisms of temporal predictive coding were characterized by decreased power of the alpha and increased power of the beta band neural oscillations in older adults during the planning phase of limb movement (Deiber, Ibañez, Missonnier, Rodriguez, & Giannakopoulos, 2013; Vaden, Hutcheson, McCollum,
Kentros, & Visscher, 2012; Zanto et al., 2011). In other studies, neural deficits during the planning phase of limb movement in older adults were characterized by age-related increase in the amplitude of ERPs prior to the onset of movement, which was associated with the slowness of motor reaction time responses (Berchicci, Lucci, Pesce, Spinelli, & Di Russo, 2012; Haaland, Harrington, & Grice, 1993; Yan, Thomas, & Stelmach, 1998). In addition, age-related modulation of ERP activation was identified as a neural correlate of diminished predictive coding mechanisms during speech production under altered auditory feedback in older adults (Li et al., 2018). Moreover, evidence from neuroimaging studies has suggested that older adults exhibit difficulties in incorporating temporal information from external sensory stimuli for motor timing coordination, and exhibit slower reaction times compared with their younger adult counterparts (Vallesi, McIntosh, & Stuss, 2009; Zanto et al., 2011). The neural substrates of such age-related changes have been identified by showing that areas within the right dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) were less activated in older vs. younger adults during movement initiation in response to temporally unpredictable sensory stimuli (Vallesi, McIntosh, & Stuss, 2009). These findings have indicated an age-related selective deterioration in sensory processing and motor timing coordination in response to stimuli with unpredictable temporal dynamics.

Although previous studies have provided new insights into the effects of normal aging on temporal predictive mechanisms of movement (Diersch et al., 2016; Diersch et al., 2013; Seidler et al., 2010; Vallesi, McIntosh, & Stuss, 2009; Zanto et al., 2011), most of these studies have focused on the limb motor system (primarily limb movement), and therefore, less is known about the effects of age-related changes in motor timing.
processing during speech production. Evidence from previous research has suggested possible anatomical overlaps between neural substrates implicated in speech and limb movement tasks by showing concurrent activation of the left inferior frontal gyrus (i.e. Broca’s area) during tasks involving speech and limb movement (Binkofski, Buccino, Stephan, et al., 1999; Gentilucci et al., 2009; Gentilucci & Volta, 2008).

The present study was motivated by the question of how normal aging would affect motor timing processing of speech and limb movement in response to temporally predictable and unpredictable sensory stimuli. By using a classical motor reaction time paradigm combined with ERP recordings, we aimed to conduct a systematic investigation to determine the effects of normal aging on the behavioral and neural correlates of temporal predictive mechanisms in the speech and limb motor systems. Based on findings of previous studies (Balci et al., 2009; Bherer & Belleville, 2004; Diersch et al., 2016; Johari et al., 2018; Seidl et al., 2010; Sterr & Dean, 2008), we hypothesized that older adults would exhibit greater decline in motor timing processing of temporally unpredictable compared to predictable sensory stimuli, as indexed by slowed motor reaction times during speech production and limb movement. In addition, previous research has led to the identification of pre-motor ERP activities over the frontal and parietal areas that were modulated by temporal characteristics of sensory stimuli (Alegre et al., 2003; Coull et al., 2016; Johari & Behroozmand, 2017a, 2018; Nobre, Correa, & Coull, 2007; Pfeuty, Ragot, & Pouthas, 2005; Walter, Cooper, Aldridge, McCallum, & Winter, 1964), and it was shown that these neural responses were increased in older adults for tasks involving speech production and limb movement (Berchicci et al., 2012; Haaland et al., 1993; Yan et al., 1998).
Based on these data, we focused on examining the pre-motor ERP correlates of speech and limb movement and hypothesized that older adults would exhibit stronger neural activities within a fronto-parietal network, reflecting their need for access to additional neural resources for motor planning and execution of movement during motor reaction time tasks. In addition, we predicted to observe differential modulation of ERPs in response to temporally predictable vs. unpredictable visual cues in younger vs. older adults, which would reflect age-related changes in the temporal predictive mechanisms that extract timing information to drive speech and limb motor reaction time responses to externally presented sensory stimuli.

6.3 Methods and Materials

6.3.1 Subjects

Fifteen younger (20 – 30 years old; mean age: 23; 7 males) and fifteen older (50 to 80 years old; mean age: 63; 8 males) adults who were native speakers of English participated in the present study. It should be noted that subjects in this study were the same as those tested in the study presented in chapters 5 of this dissertation. All subjects reported no history of psychiatric, neurological or speech disorder, and had normal hearing and normal (or corrected) vision. Handedness of subjects was assessed using the Edinburgh handedness inventory (Oldfield, 1971), and all were right handed (score range 72-100). All study procedures, including recruitment, data acquisition and informed consent were approved by the University of South Carolina Institutional Review Board, and subjects were monetarily compensated for their participation.
6.3.2 Experimental Design

The experiment was conducted in a sound attenuated booth in which subjects performed the speech and limb movement tasks while EEG signals were recorded. Note that in this study, the terms speech production and limb movement are used to refer to vowel vocalization and button press tasks, respectively. During each task, subjects were instructed to prepare for the cued movement and start vocalizing a steady speech vowel sound /a/ or pressing a button with the index finger of their dominant (i.e. right) limb after a circle (go signal) appeared on the screen and to stop when the circle disappeared (see Figure 3.1 in chapter 3). We designed two counterbalanced blocks within which subjects performed the speech and limb movement tasks in a randomized order: 1) a temporally-predictable block, in which there was a fixed time interval of 1500 ms between the onset of the visual cue and go signal and 2) a temporally-unpredictable block in which the time interval between visual cue and go signal was randomized between 1000-2000 ms using a linear distribution. During each block, a total number of 220 trials were collected, with approximately 110 trials for speech and 110 trials for limb movement. The inter-trial-interval (ITI) was 2-3 seconds in each block and subjects took a 5-minute break between two blocks. All the experimental parameters, including the order of the tasks, conditions, visual cues, go/stop signals, and the stimulus timing intervals were controlled by a custom-made program implemented in Max/Msp 5.0 program (Cycling ’74). Subjects’ responses including speech vowel sound vocalizations and button presses were recorded at 44.1 KHz on a laboratory computer for the analysis of the motor reaction times and time-locked averaging of the ERP responses in each experimental condition.
6.3.3 Behavioral and EEG Data Acquisition

The speech signal was picked up using a head-mounted AKG condenser microphone (model C520), amplified by a Motu Ultralite-MK3, and delivered to subjects through Etymotic insert earphones (model ER-1). The onset of speech vowel vocalizations was detected using a voice onset detector algorithm in Max/Msp, and the onset of button presses were registered at the time when subjects pressed the button in response visual cue stimuli. The onsets of speech and limb movement triggered TTL pulses that were generated by Max/Msp, and these TTL pulses were simultaneously recorded in the EEG file for time-locked averaging of ERP activities in response to the onset of speech and limb movement. The EEG signals were recorded from 64 electrodes on the subjects’ scalp using the Brain Vision active electrode system (Brain Products GmbH, Germany) placed on a standard electrode cap (Easy-Cap GmbH, Germany). The electrode placement on the cap followed the standard 10-20 montage and the EEG signals were recorded using a common reference. A BrainVision actiCHamp amplifier (Brain Products GmbH, Germany) on a computer utilizing Pycorder software recorded the EEG signals at 1 kHz sampling rate after applying a low-pass anti-aliasing filter with 200 Hz cut-off frequency.

6.3.4 Reaction Time Analysis

A custom-made MATLAB code was used to obtain measures of reaction time during speech production and limb movement for both younger and older adults. Reaction times for speech production and limb movement were calculated by the time difference between the onset of the “Go” cues and the initiation of speech and limb
movement responses, respectively. We verified that the error rates of inconsistent motor responses (e.g., pressing a button instead of vocalizing or vice versa) were below 5% for both younger and older adults, and those erroneous trials we excluded from data analysis. For statistical analysis, measures of speech and limb motor reaction times were submitted to a mixed ANOVA model with the group age (older vs. younger adults) as a between-subjects factor, and stimulus timing (predictable vs. unpredictable) and modality (speech vs. limb) as within-subjects factors.

6.3.5 EEG Analysis

The EEGLAB toolbox (Delorme & Makeig, 2004) was used to analyze the recorded EEG signals in order to extract ERPs time-locked to the onset of speech production and limb movement during temporally predictable and unpredictable conditions for both age groups. The recorded EEGs were first band-pass filtered using a standard EEGLAB FIR filter with cut-off frequencies set to 1 and 30 Hz (−24 dB/oct). Independent Component analysis (ICA) was applied to remove eye movement, blinks, muscle, and line noise artefacts. Following ICA, the EEG signals were segmented into epochs ranging from −500 ms before and 500 ms after the onset of speech production and limb movement. Since the choice of the band-pass filter with its high-pass cut-off at 1 Hz would automatically remove DC offsets from EEG data and would make baseline correction obsolete (Maess, Schröger, & Widmann, 2016; Widmann, Schröger, & Maess, 2015), we did not implement a separate baseline correction procedure. This approach was specifically helpful to analyze EEG data in the pre-motor time window without artificially aligning EEG activities to a pre-defined baseline period before the onset of speech and limb movement responses. The extracted epochs were then averaged across
all trials separately for each condition (predictable vs. unpredictable) to obtain ERP responses for speech and limb movement onset during predictable and unpredictable blocks for both age groups separately. A minimum number of 100 trials for each condition were used to calculate ERP responses for each individual subject. The extracted ERP profiles were then averaged across all subjects to calculate the grand-average ERP responses.

The extracted ERP components in response to speech and limb movement initiation were separately analyzed within 6 regions of interests (ROIs) that included electrodes over the frontal (F), frontocentral (FC), frontotemporal (FT), central (C), centroparietal (CP), parietal (P) areas. In our previous studies (Johari & Behroozmand, 2017a, 2018), we found that 50 ms time windows are sensitive enough to capture the dynamic nature of ongoing motor timing processing of sensory stimuli during the preparatory phase of speech and limb movement. Therefore, in the present study, ERP amplitudes were extracted for 10 pre-motor time windows from -500 to 0 ms time windows with 50 ms duration. For each time window, neural responses were measured as the mean amplitude of ERP responses in two electrodes in the left (e.g., left frontocentral: FC1 and FC5) and two electrodes in the contralateral right side for each ROIs (e.g., right frontocentral: FC2 and FC6). In each pre-motor time window, mixed ANOVA models were performed using SPSS v.24 for each ROI to examine the effects of age group (young vs. old adults) as a between-subjects factor, and stimulus timing (predictable vs. unpredictable), modality (speech vs. limb), and laterality (left vs. right) as within-subjects factors on pre-motor ERP activities. The p-values were adjusted for the number of time
windows using Bonferroni’s correction for multiple comparisons. The partial eta squared
($\eta^2$) was used to report effect size for the main effects and interactions.

6.4 Results

6.4.1 Motor Reaction Time

The bar plot representation of the behavioral measures of motor reaction time are
shown in Figure 6.1. The statistical analysis yielded significant main effects of group
($F_{(1,28)} = 4.27, p < 0.05, \text{partial } \eta^2 = 0.13$), timing ($F_{(1,28)} = 14.67, p < 0.001, \text{partial } \eta^2 =
0.34$), and modality ($F_{(1,28)} = 15.76, p < 0.001, \text{partial } \eta^2 = 0.36$), and these effects were
qualified by a significant group $\times$ timing $\times$ modality interaction ($F_{(1,28)} = 4.60, p = 0.04,$
partial $\eta^2 = 0.14$). Follow-up analysis for speech movement revealed significant main
effects of timing ($F_{(1,28)} = 8.17, p < 0.01, \text{partial } \eta^2 = 0.22$), group ($F_{(1,28)} = 7.12, p < 0.05,$
partial $\eta^2 = 0.20$), and timing $\times$ group interaction ($F_{(1,28)} = 6.06, p < 0.05, \text{partial } \eta^2 =$
0.17). Post-hoc analysis revealed that older adults were significantly slower than younger
adults during speech production in response to temporally unpredictable stimuli ($t_{(28)} = 
3.23, p < 0.01$), but no such effect was observed for the predictable stimuli ($t_{(28)} = 0.26, p$
= 0.79). Follow-up analysis for limb movement revealed a significant effect of timing
($F_{(1,28)} = 7.89, p < 0.01, \text{partial } \eta^2 = 0.22$) with faster motor reaction times in response to
temporally predictable compared with unpredictable sensory stimuli. However, there was
no significant effect of group ($F_{(1,28)} = 0.70, p = 0.40, \text{partial } \eta^2 = 0.02$), nor a timing $\times$
group interaction ($F_{(1,28)} = 0.01, p = 0.90, \text{partial } \eta^2 = 0.001$) on motor reaction times
during limb movement.
Figure 6.1 Illustrates the motor reaction times in younger and older adult for initiation of A) speech and B) limb movement initiation in response to temporally predictable and unpredictable stimuli.

6.4.2 ERP Results

Results of the analysis for ERP responses to temporally predictable and unpredictable stimuli are shown in Figures 6.2 and 6.3, respectively for speech production and limb movement. In these figures, the overlaid profiles of ERP activities for younger vs. older adults are shown in panels A and C for temporally predictable and unpredictable conditions, respectively. The topographical distribution maps are plotted for 64 electrodes within 10-time windows from -500 to 0 ms prior to the onset of speech and limb movement in panels B and D for temporally predictable and unpredictable stimuli, respectively. For both speech and limb movement, prominent ERP activities were identified over the bilateral frontal and parietal areas in response to temporally predictable and unpredictable sensory stimuli.
Statistical analysis for pre-motor ERP activities revealed a significant group × timing × modality interaction over the frontal ($F_{(1,28)} > 6.58, p < 0.01, \eta^2 > 0.21$) and parietal electrodes ($F_{(1,28)} > 5.60, p < 0.02, \eta^2 > 0.19$) within two time windows from -150 to -50 ms. Follow-up analysis for these time windows revealed significant timing × group interactions for speech production over the frontal ($F_{(1,28)} > 7.67, p < 0.01, \eta^2 > 0.23$) and parietal ($F_{(1,28)} > 6.45, p < 0.02, \eta^2 > 0.20$) areas. Post-hoc analysis showed that pre-motor ERP activities before the onset of speech were significantly larger for older vs. younger adults in response to unpredictable stimuli ($t_{(28)} > 2.5, p < 0.03$), but no such effect was observed for predictable stimuli ($t_{(28)} < 0.68, p > 0.5$) (Figure 6.4, Panels A and C). However, follow-up analysis for limb movement did not reveal a significant timing × group interaction over the frontal and parietal areas ($F_{(1,28)} < 0.88, p > 0.36, \eta^2 < 0.03$) (Figures 6.4, panels B and D). In addition, we found a significant main effect of laterality, indicating stronger pre-motor ERP activities in the left vs. right hemisphere for limb movement over the parietal area within time windows from -100 to 0 ms ($F_{(1,28)} > 7.87, p < 0.01, \eta^2 > 0.23$).

6.5 Discussion

In the present study, we conducted a systematic investigation to determine the effects of normal aging on the temporal predictive mechanisms in the motor system by examining pre-motor ERP components of speech and limb movement in response to temporally predictable and unpredictable sensory (i.e. visual) stimuli. Previous studies in younger adults have shown that temporal predictability of sensory stimuli can modulate ERP activities prior to the onset of speech and limb movement (Alegre et al., 2003; Johari & Behroozmand, 2017a, 2018).
Figure 6.2 Panels A and C display the overlaid temporal profiles of ERPs for older (red line) vs. younger (black line) adults during speech motor reaction time task in response to temporally predictable and unpredictable conditions, respectively. In these plots, ERP responses are shown for six different regions of interests in time windows spanning -500 ms before to 500 ms after the onset of speech movement initiation. Panels B and D show the topographical scalp distribution maps of pre-motor ERP activities for younger (top row) and older (bottom row) adults for speech motor responses to temporally predictable and unpredictable stimuli, respectively. In these plots, topographical distribution maps are shown in 10 time windows from -500 to 0 ms before the onset of speech movement initiation (each window at 50 ms).
Figure 6.3 Panels A and C display the overlaid temporal profiles of ERPs for older (red line) vs. younger (black line) adults during limb motor reaction time task in response to temporally predictable and unpredictable conditions, respectively. In these plots, ERP responses are shown for six different regions of interests in time windows spanning -500 ms before to 500 ms after the onset of limb movement initiation. Panels B and D show the topographical scalp distribution maps of pre-motor ERP activities for younger (top row) and older (bottom row) adults for limb motor responses to temporally predictable and unpredictable stimuli, respectively. In these plots, topographical distribution maps are shown in 10 time windows from -500 to 0 ms before the onset of limb movement initiation (each window at 50 ms).
Figure 6.4 Profiles of the mean amplitude of ERPs across older (red line) and younger (black line) adults (n = 15 per group) in 10 different time windows before the onset of speech and limb movement in response to temporally predictable and unpredictable stimuli for electrodes over the frontal and parietal areas. In these plots, each circle represents the mean amplitude of ERPs for a 50 ms time window. Significant between-groups differences (p < 0.05, Bonferroni corrected) are marked by asterisks (*) in each panel.
These pre-motor neural activities have been suggested as neurophysiological biomarkers of the temporal predictive code in the motor system that plays a critical role in extracting timing information from sensory stimuli to drive behaviorally relevant motor responses (Johari & Behroozmand, 2017a, 2018). In this study, we utilized a motor reaction time paradigm to address the question as to how normal aging may affect the behavioral and neural correlates of the temporal predictive mechanisms for speech production and limb movement in two groups of older and younger adults. Results of our analysis revealed a temporal and modality-specific decline in the preparatory mechanisms of movement in older adults by showing age-related increases in pre-motor ERP activities for speech production (but not limb movement) only in response to temporally unpredictable sensory stimuli. Our data also showed that such age-related modulation of ERP activities was associated with increased (slower) motor reaction times for speech responses to unpredictable stimuli. These findings suggest that motor timing processing of speech is compromised in older adults and that the aging brain calls for the engagement of additional neural mechanisms to prepare and execute motor commands for speech production in response to sensory stimuli with unpredictable timing intervals.

6.5.1 Effects of Normal Aging on Movement Reaction time

Our behavioral findings revealed that in response to temporally unpredictable stimuli, motor responses were significantly slower (longer reaction times) in older vs. younger adults only during speech production but not limb movement initiation. In contrast, for temporally predictable stimuli, motor response reaction times were not significantly different in older vs. younger adults during both speech and limb movement initiation. These findings confirmed our hypothesis that older adults would exhibit greater
decline in motor timing processing of temporally unpredictable sensory stimuli, and 
进一步验证了前人研究中涉及的言语和躯体运动系统（Chauvin et al., 2016; Johari et al., 2018）。这些数据支持了这样的观点，即 
说话和肢体运动的运动节律处理机制在正常老化的背景下对具有可预测时间规律的感官刺激的反应中是未被损害的。

对于对时间上不可预测的刺激反应的运动反应时间，我们的数据表明，正常衰老对于言语运动的反应时间较慢，而对肢体运动没有这种现象。这种特定的模态差异在运动节律处理中的表现，可能由运动生产机制的内在差异所解释。在我们的实验范式中按按钮需要激活一组肌肉来进行肢体运动，而进行语音元音发声任务则是在呼吸系统、喉部系统和发音系统中，以精确地、协调地、分块地激活更大一组肌肉来完成。此外，获取元音的音位表示再生成运动表示可能需要更多的认知资源参与计划阶段的说话运动。因此，一个衰老的大脑可能会在对不可预测刺激（即无法预知的刺激）的感官刺激反应中，运动时序处理上受到损害，因为这些需要更多的神经
resources for processing than those in response to temporally predictable cues. The reduced capacity for processing timing information in unpredictable sensory stimuli and a diminished ability for translating it into a temporal predictive code may explain why motor timing processing of speech is deteriorated in older adults, who exhibited slower reaction times during vowel vocalizations than their younger counterparts. Further supporting evidence for age-related decline of temporal processing mechanisms is provided by findings of previous studies showing an increased error rate during temporal estimation, discrimination, motor reproduction, and judgement of unpredictable timing intervals in older vs. younger adults (Balci et al., 2009; Zanto et al., 2011).

6.5.2 Effects of Normal Aging on Neural Correlates of Movement Preparation

Results of our analysis on ERP responses showed that the pre-motor ERP activities before speech and limb movement onset were not different in older vs. younger adults in response to temporally predictable sensory stimuli. In line with our behavioral data, this latter evidence at the neural level further supports the notion that the underlying neural mechanisms of motor timing processing are spared in normal aging when sensory stimuli are temporally predictable. However, when movement was generated in response to unpredictable stimuli, the amplitude of the pre-motor ERP activities was significantly increased in older vs. younger adults for speech production, though no such effect was observed during limb movement. In conjunction with our behavioral data, this latter evidence at the neural level corroborated the notion that normal aging is associated with modality-specific decline of speech motor timing processing in response to unpredictable stimuli, as indexed by an age-related increase in pre-motor ERPs in older vs. younger adults.
Previous studies on the mechanisms of timing processing during a wide range of memory, cognitive, and action observation or prediction tasks have identified the “Contingent Negative Variation” (CNV) component, which is an ERP activity elicited before the onset of an imperative signal that reflects how the brain encodes the timing of an upcoming sensory stimulus for establishing a temporal predictive coding mechanism (Diersch et al., 2013; Pfeuty et al., 2005; Walter et al., 1964). Since the pre-motor ERP activities elicited before the onset of speech and limb movement in the present and previous studies (Alegre et al., 2003; Johari & Behroozmand, 2017a, 2018; Kuhn et al., 2004) share common characteristics with the CNV response component (e.g., latency, amplitude, and topographical morphology), it is reasonable to propose that these observed pre-motor ERP responses reflect a similar temporal predictive coding mechanism that extracts timing information from sensory stimuli and prepares and drives motor actions (e.g., speech or limb movement) in response to events with predictable or unpredictable temporal characteristics. Our current data provide supporting evidence for this proposal by showing that age-related modulation of pre-motor ERPs was associated with age-related decline in preparatory neural mechanisms of motor timing processing in response to externally presented sensory stimuli. In this context, results of our study are indicative of modality-specific decline of neural mechanisms that support temporal predictive coding of unpredictable sensory stimuli during speech production, leading to slower motor reaction time responses in older adults.

A possible account of the age-related increase in pre-motor ERP activations in our study is that an older brain may recruit additional neural resources to compensate for the decline of the cognitive and sensorimotor mechanisms of speech motor timing...
processing. As suggested by our data, such an age-related effect was reflected in the slowed motor reaction times in response to unpredictable sensory stimuli, accompanied by increased pre-motor ERP activations during speech production in older adults. Studies in patients with Parkinson’s disease (PD) have reported that multiple brain regions including the premotor/motor cortex, supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), and cerebellum are overactivated, especially during speech, to compensate for deficits in dopamine-dependent mechanisms of motor timing processing as a result of basal ganglia pathology (Liotti et al., 2003; Narayana et al., 2009; Sachin et al., 2008; Wu & Hallett, 2005; Yu, Sternad, Corcos, & Vaillancourt, 2007). The significant role of the basal ganglia network and its underlying dopamine transmission mechanisms have been associated with fine-tuned regulation of movement timing in previous studies (Coull, Cheng, & Meck, 2011; Matell & Meck, 2004; Tomassini, Ruge, Galea, Penny, & Bestmann, 2015).

Although not as extensive as in PD, studies on neurologically intact older adults have demonstrated atrophy of dopaminergic neurons in fronto-basal ganglia networks (Bäckman et al., 2000; Balci et al., 2009; Merchant, Harrington, & Meck, 2013; Mozley, Gur, Mozley, & Gur, 2001; Rubin, 1999; Volkow et al., 1998). Based on findings of these previous studies, we suggest that normal aging is associated with recruiting compensatory neural mechanisms similar to those in PD to counteract age-related decline of motor timing processing. In the context of the temporal compensation theory (Turgeon, Lustig, & Meck, 2016), older adults are able to perform low-demand (i.e. simple) motor timing tasks similar to what is performed by their younger counterparts. However, for high-demand tasks that require processing beyond the level of available
neural resources, the older brain can use compensatory mechanisms to ameliorate age-related decline in temporal processing of sensory stimuli during movement production. In this study, we found that pre-motor ERP activities over the frontal areas were increased in older vs. younger adults when subjects produced speech movement in response to temporally unpredictable sensory stimuli. This age-related modulation of frontal ERPs during speech production may be a neural indicator of compensatory mechanisms for fronto-basal ganglia dysfunctions in older adults. This notion is further corroborated by results of a recent neuroimaging study showing overactivation of BOLD responses in the right motor cortex in older vs. younger adults during speech motor timing tasks (Tremblay, Sato, & Deschamps, 2017), suggesting that older adults may recruit additional neural resources to compensate for functional decline during speech production. In addition, Tremblay et al. (Tremblay et al., 2017) showed that overactivation of the right posterior cingulate cortex in older adults was indicative of compensatory mechanisms and the need for allocating higher levels of cognitive resources to counteract age-related decline during speech production tasks. In the present study, we found a consistent pattern of increased ERP activation in the frontal regions, which may similarly highlight the neural signatures of such cognitive-related compensatory mechanisms during speech production in older adults. However, our data showed that recruiting such compensatory mechanisms at the neural level may not necessarily translate into boosting the behavioral performance and improving speech motor reaction times in older adults in response to temporally unpredictable sensory stimuli. As discussed earlier, this effect may be due to the older adults’ potential inability to recruit sufficient neural resources even after activating compensatory mechanisms to
perform a high-demand speech task that requires coordinated movement of a large group of muscles in multiple functionally independent systems (e.g., respiratory, laryngeal, and articulatory) in response to sensory stimuli with unpredictable temporal patterns.

The absence of behavioral and ERP differences between older and younger adults during the button press task in the present study was not consistent with findings of previous studies that showed slower motor reaction time (Vallesi, McIntosh, & Stuss, 2009; Zanto et al., 2011) and reduced activation of neural responses during limb movement in older vs. younger adults (Barrett, Shibasaki, & Neshige, 1986; Loveless & Sanford, 1974; Stewart, Tran, & Cramer, 2014; Yordanova, Kolev, Hohnsbein, & Falkenstein, 2004). This inconsistency may partially be attributable to the differences between the experimental tasks implemented in the present compared with previous studies. In this study, the limb motor reaction time task involved a button press condition that was simpler to perform than the motor selection and limb movement tasks used in previous studies (Dirnberger et al., 2000; Stewart et al., 2014; Yordanova et al., 2004). For example, Stewart et al. (Stewart et al., 2014) showed that diminished behavioral performance during an action selection task was associated with deactivation of the primary motor cortex in older adults, but no such effect was examined in younger adults as a control group. In addition, the timing intervals between the warning and imperative signals were not similar in the present and those previous studies, and we also used two blocks of predictable and unpredictable conditions in which subjects responded to visual cues during speech and limb motor reaction time tasks. Furthermore, the present study used different age groups than those used in previous studies for examining the behavioral and neural correlates of movement timing in older and younger adults.
Altogether, the differences in the experimental paradigm and characteristics of recruited subjects may explain inconsistencies related to the effect of normal aging on the behavioral and neural mechanisms of speech production and limb movement in older vs. younger adults between the present and previous studies.

In addition to the pre-motor ERP modulation over the frontal areas, our data revealed a similar effect of normal aging on pre-motor ERP activities over the parietal areas during speech responses to temporally unpredictable sensory stimuli. In line with this finding, previous fMRI studies have identified neural mechanisms within the parietal cortex that are involved in differential neural processing of temporally predictable vs. unpredictable sensory stimuli (Coull et al., 2016; Nobre et al., 2007). Based on findings of these previous studies, it has been proposed that the parietal cortex subserves a dual-mode processing mechanism in which the brain establishes a temporal expectancy model for estimating the timing of upcoming predictable sensory stimuli, and for temporally unpredictable stimuli, it recruits a hazard function in which the likelihood of occurrence for an upcoming sensory stimulus increases as time elapses. In the context of this dual-mode processing model, we suggest that the absence of a difference between pre-motor ERPs over the parietal areas in older vs. younger adults in this study indicates that the neural mechanisms of temporal expectancy are unaffected by normal aging during speech production and limb movement in response to temporally predictable sensory stimuli. However, increased pre-motor ERP activities in older adults over the parietal area suggests an age-related decline of the neural mechanisms underlying the hazard function in normal aging, which may subsequently lead to less accurate estimation of timing.
information in response to unpredictable stimuli and slowed motor reaction times, particularly during speech production.

6.5.3 Limitations

A potential limitation of the present study is that it did not probe the effects of gender-specific differences on age-related changes in motor preparatory mechanisms of speech production and limb movement. In one previous study (Li et al., 2018), it has been shown that males generate stronger N1 and P2 ERP components compared with females during speech production, however, females were shown to generate faster N1 ERP responses compared to male speakers. While we did not include gender as a factor of interest for data analysis in the present study, it is important to note that inherent gender-specific characteristics may have differential effects on age-related changes in the behavioral and neural mechanisms of speech and limb movement. Therefore, further research is warranted to conduct systematic examination on the effect of gender on the mechanisms of speech and limb movement in normal aging.

Another limitation of the present study is the lack of control conditions for ruling out the effect of visual-evoked neural responses to the “go” cues (i.e. the onset of the black circles on the screen) from the pre-motor time windows. However, examination of our data suggests that the observed differences in pre-motor neural activities are not accounted for by differences in neural processing of the “go” visual cue stimuli as the ERP responses are qualitatively different between motor conditions, with characteristics consistent with responses associated with speech versus limb movements, while the visual “go” cue signal (i.e. the onset of a black circle on the screen) remains constant.
between age groups or predictable vs. unpredictable timing conditions. This is verified by comparing pre-motor neural activities for speech vs. limb movements in response to predictable stimuli. Since the measures of motor reaction time were not significantly different for these conditions within age groups, we can directly compare them and it is reasonable to hypothesize that if the calculated ERPs were reflective of visual-evoked activities, such neural responses would be elicited with nearly identical response profiles for speech and limb movement because in that case the stimulus in both conditions was the onset of a black circle (“go” cue) that appeared ~400 ms before the onset of the motor response. However, as shown in our data, time-locked ERP responses to the onset of speech vs. limb movement show different patterns of neural activations that are indexed by the differences in latency, amplitude, and the overall spatio-temporal profiles of neural activation patters for these different conditions.

In general, pre-motor ERP responses to speech movement emerged earlier than responses to limb movement and represented a more smooth deflection of potentials with smaller amplitudes compared with the sharp and large amplitude pattern of deflection for limb movement. In addition, topographical distribution maps of these responses follow the pattern of pre-motor rather than visual evoked potentials and suggest the presence of a hypothetical dipole in pre-motor and motor cortex with a negative polarity component over the fronto-central electrodes and its inverted (positive) polarity over the parietal area (as compared with visual-related dipoles with potentials over the posterior occipital electrodes). Moreover, since the ERP responses were calculated time-locked to the onset of speech and limb movement, the inherent trial-by-trial jitter in the measures of motor reaction time will likely have led to the cancellation of out-of-phase visual evoked
responses in the pre-motor time window examined in this study. This notion is further corroborated by the observation that the pre-motor responses to the onset of speech and limb movement are preceded by a relatively flat baseline activity at latencies ~400 ms before the onset of pre-motor ERP activities. Based on these observations, we argue that the observed differences in neurophysiological responses to speech vs. limb movement are in fact driven by differences in pre-motor neural processing mechanisms underlying these different motor functions, rather than by differences in visual evoked responses to the onset of the “go” cues presented on the screen. Since the current study was primarily motivated by the question as to how normal aging affects the pre-motor mechanisms of motor timing during speech production and limb movement, limiting our analysis to the pre-cue time window was not possible because the inherent trial-by-trial jitter in motor reaction time would have led to the cancellation of pre-motor responses that were elicited prior to the onset of movement. Therefore, we aimed to examine ERP response profiles that were time-locked to the onset of motor responses to temporally predictable and unpredictable visual cue stimuli between the young and old adults during speech production and limb movement tasks.

Lastly, although previous studies have shown that modulation of band-specific power of neural oscillations (e.g., alpha or beta) are reflective of top-down predictive coding mechanisms, examining the effects of normal aging on these neural oscillatory mechanisms was beyond the scope of the present study and its hypotheses. Future studies are warranted to investigate the age-related modulation of band-specific neural responses and their association with predictive coding mechanisms during speech and limb motor
reaction time tasks in response to sensory stimuli with predictable and unpredictable temporal characteristics.

6.6 Conclusion

Our findings indicate that timing processing mechanisms of speech and limb motor systems are spared in normal aging when older adults generate movement in response to temporally predictable sensory stimuli. In contrast, we found age-related decline in motor timing processing of speech in response to unpredictable stimuli, as indexed by slower motor reaction times and increased amplitude of pre-motor ERP activities in older vs. younger adults. We conclude that the aged brain relies on compensatory neural mechanisms to offset age-related functional decline in motor timing processing of speech in response to unpredictable sensory stimuli. However, due to limitations imposed by task demands and reduced capacity of cognitive and sensorimotor resources, recruiting such compensatory mechanisms at the neural level may not immediately translate into improved behavioral performance of speech motor timing processing in older adults. To our knowledge, this is the first study to systematically investigate the behavioral and neural correlates of normal aging effects on speech and limb motor timing processing in a unified framework. Future studies will further elucidate the effects of normal aging by using advanced techniques to map out the brain networks involved in neural processing of motor timing in the speech and limb modalities.
Chapter 7

General Discussion and Conclusion
In the five studies presented in previous chapters of this dissertation, the behavioral and neural correlates of temporal predictive mechanisms were investigated during initiation and inhibition of speech production and limb movement in healthy younger and older subjects. In this chapter, the general discussion and conclusion will be provided about the findings in this dissertation.

7.1 Behavioral and Neural Correlates of Temporal Predictive Codes in Healthy Young Subjects

7.1.1 Temporal Predictive Codes During Speech and Limb Movement Initiation and Inhibition

The behavioral findings in young healthy adults (see chapter 2) showed that motor reaction times were faster in response to temporally predictable vs. unpredictable sensory stimuli during initiation and inhibition of speech and limb movement. These findings are consistent with findings of previous studies (Bevan et al., 1965; Vallesi, McIntosh, Shallice, et al., 2009) and provide further support for a predictive coding mechanism that enables the motor system to process temporal regularity (predictability) to generate faster movements. In the context of the internal forward model theory (Witney et al., 1999; Wolpert, 1997; Wolpert et al., 2011; Wolpert & Flanagan, 2001; Wolpert et al., 2001), the findings suggest that temporally-predictable sensory stimuli result in the establishment of more robust feedforward motor representations during movement. As suggested by previous studies (Miall & Wolpert, 1996; Wolpert & Flanagan, 2001), the internal forward model can learn, reinforce, and internally simulate temporal
relationships between motor commands and sensory stimuli. The behavioral findings in young healthy subjects suggest that feedforward motor mechanisms are enhanced, and the contribution of sensory feedback is reduced for processing temporally-predictable stimuli, leading to faster movement with shorter reaction times.

These findings not only support previous research (Bevan et al., 1965; Vallesi, McIntosh, Shallice, et al., 2009) in limb movement but also suggest the existence of common temporal mechanisms for speech and limb movement. To be specific, the findings suggest that temporal predictive mechanisms may not be modality specific by demonstrating that predictability of sensory stimuli accelerates both speech and limb movement. In addition, findings may indicate that common temporal predictive mechanisms subserve movement initiation and inhibition by showing that initiation and inhibition of movement was faster in response to temporally predictable sensory stimuli. Overall behavioral findings in younger adults support the existence of common temporal predictive mechanisms for initiation and inhibition of speech and limb movement.

7.1.2 Neural Correlates of Temporal Predictive Mechanisms During Initiation of Speech and Limb Movement

The findings in chapter 3 showed that ERPs prior to onset speech and limb movement initiation were significantly attenuated in response to temporally predictable vs. unpredictable stimuli. The suppression of premotor neural activities in response to temporally-predictable stimuli can be discussed in the framework of the internal forward model (Witney et al., 1999; Wolpert et al., 2011; Wolpert & Flanagan, 2001). According to this model, the efference copies of motor commands are translated into internal
predictions that estimate the current and future states of the motor system and make adjustments when errors occur in sensory feedback associated with self-generated movements. Studies have demonstrated that these internal predictive signals can suppress neural activities in response to sensory stimuli triggered by button press (Chen et al., 2012; Mifsud et al., 2016; Timm et al., 2016) or self-produced speech (Aliu, Houde, & Nagarajan, 2009; Behroozmand & Larson, 2011; Behroozmand et al., 2011; Behroozmand et al., 2016; Chang et al., 2013; Heinks-Maldonado, Mathalon, Gray, & Ford, 2005; Ventura, Nagarajan, & Houde, 2009). This motor-induced suppression effect has been proposed to account for a reduced contribution of sensory mechanisms for processing incoming stimuli. In addition, other studies have provided evidence that the internal predictive signals may enhance temporal processing of sensory information (Conradi et al., 2016), and lead to greater suppression of neural activities in response to temporally-predictable compared with unpredictable sensory stimuli (Behroozmand et al., 2011; Behroozmand et al., 2016; Chen et al., 2012). These findings indicate that during movement initiation, a more robust temporal predictive code can be established internally to provide an accurate estimate of timing for sensory stimuli that follow a temporally-regular (predictable) pattern. The behavioral consequence of this effect is to drive motor behavior with shorter reaction times in response to temporally-predictable compared with unpredictable sensory stimuli (Bevan et al., 1965; Niemi & Naatanen, 1981; Vallesi, McIntosh, Shallice, et al., 2009).

The ERP findings for speech and limb movement initiation may suggest that the sensorimotor integration mechanisms are responsible for suppression of neural activities for temporally-predictable sensory stimuli that are encoded by the internal feedforward
neural representations. By contrast, unpredictable stimuli with irregular temporal
dynamics require the allocation of more neural resources to process sensory information
for speech and limb movement production. The correlation findings between ERP
amplitudes and motor reaction times further support the notion that temporal
predictability of sensory stimuli can enhance internal predictions about when to initiate
speech and limb movement. Overall, these findings suggest that pre-movement ERPs are
robust neurophysiological biomarkers of temporal predictive mechanisms in the speech
and hand motor systems.

7.1.3. Neural Correlates of Temporal Predictive Mechanisms During Initiation and
Inhibition of Speech Production and Limb Movement

In chapter 4, the neural correlates of temporal mechanisms of movement initiation
and inhibition (cessation) were examined during speech and limb movement. For limb
movement initiation and cessation, premotor ERPs emerged as a positive-polarity
potential with a left-lateralized centroparietal distribution, which were attenuated in
response to predictable compared with unpredictable sensory stimuli. For speech
movement initiation, ERPs emerged as bilateral negative-polarity potentials over the
centroparietal electrodes, which similar to limb movement, were attenuated in response to
predictable compared with unpredictable sensory stimuli. In contrast, speech cessation
elicited a different pattern of premotor neural activity that emerged as a bilateral positive-
polarity ERP component over the centroparietal electrodes with stronger activities for
predictable compared with unpredictable. The difference in temporal-specific pattern of
neural activity modulation for speech initiation and cessation may indicate that the motor system utilizes distinctive neural processing mechanisms to process timing information for execution and termination of more complex movements such as speech production. However, a potential limitation of the implemented experimental paradigm in this study was that movement cessation responses to stop signals were followed by their initiation after the onset of go cues within the speech and hand motor modalities. Although modality within predictable and unpredictable blocks were randomized to minimize the effect associated with movement task orders (initiation vs. cessation), it should be noted that one should be cautious to draw strong conclusions related to the observed differences between movement initiation and cessation effects.

Overall, these findings are in line with the results of previous sections (7.1.1 and 7.1.2) and may indicate that sensorimotor mechanisms can extract and incorporate external timing information for both initiation and cessation of the movement to establish temporal predictive codes that subsequently can accelerate motor response. Moreover, ERPs prior to onset of speech and limb movement initiation and cessations may be neural signatures of temporal predictive codes in the motor system, even though speech and limb movement cessation show relatively different patterns of ERPs in response to temporally predictable vs. unpredictable stimuli.

7.2 Age-related Changes in Behavioral and Neural Correlates of Temporal Predictive Mechanism During Speech Production and Limb Movement

7.2.1 Normal Aging Effects on Motor Reaction Times During Speech and Limb Movement Initiation and Inhibition
In chapter 5, the normal aging effects on motor reaction were investigated during initiation and inhibition of speech and limb movement. Findings showed that older adults were significantly slower than younger adults during speech initiation and inhibition when stimulus timing was unpredictable. In contrast, older adults’ performance was comparable to younger adults during limb movement initiation and inhibition regardless of stimulus timing.

The older adults’ slower motor reaction times for temporally unpredictable stimuli may be discussed in the context of temporal expectancy and the hazard function (Coull et al., 2016). It has been suggested that the brain uses a hazard function to process temporally unpredictable intervals, whereas temporal expectancy supports the processing of predictable intervals (Coull et al., 2016). Based on our findings, we suggest that aging is associated with decline of the hazard function, which can consequently lead to less precise estimates about the timing of upcoming imperative signals for movement initiation and inhibition during unpredictable timing. In contrast, temporal expectancy mechanisms are preserved for movement production in aging, suggesting that similar to younger adults, older subjects can use temporally predictable information to establish expectancy about the timing of an upcoming imperative signal and accelerate their motor response reaction time.

The finding that younger adults were faster than older adults in response to temporally unpredictable speech stimuli may also reflect age-related changes in processing of complex sensory-motor stimuli. Older adults may experience increased difficulties in processing temporal information during a complex and more cognitively demanding sensory-motor task compared with younger adults, partially due to their
limitation in allocation of neural resources during information processing for stimuli with unpredictable temporal patterns (Jordan & Rabbitt, 1977; Ma & Trombly, 2004). In this study, fixed timing was used for temporally predictable stimuli during the motor reaction time task and this enabled subjects to establish a stronger temporal expectancy about the timing of the upcoming imperative signal. In contrast, timing variability in the unpredictable condition may have resulted in an increase in the level of complexity for temporal information processing, leading to diminished cognitive and sensorimotor performance in older adults compared with their younger counterparts.

7.2.2 Neural Correlates of Age-related Changes During Speech and Limb Movement Initiation

The findings in chapter 6 showed that pre-motor neural activities before speech and limb movement onset were not different in older vs. younger adults in response to temporally predictable sensory stimuli. In line with our behavioral data (see above), this latter evidence at the neural level further supports the notion that the underlying neural mechanisms of motor timing processing are spared in normal aging when sensory stimuli are temporally predictable. However, when movement was generated in response to unpredictable stimuli, the amplitude of the pre-motor ERP activities was significantly increased in older vs. younger adults for speech production, though no such effect was observed during limb movement. In conjunction with our behavioral data, this latter evidence at the neural level corroborated the notion that normal aging is associated with modality-specific decline of speech motor timing processing in response to unpredictable
stimuli, as indexed by an age-related increase in pre-motor ERPs in older vs. younger adults.

This selective decline in temporal predictive mechanisms can be explained by temporal compensation theory (Turgeon, Lustig, & Meck, 2016). Normal aging is associated with recruiting compensatory neural mechanisms similar to those in PD to counteract age-related decline of motor timing processing. In the context of the temporal compensation theory (Turgeon, Lustig, & Meck, 2016), older adults are able to perform low-demand (i.e. simple) motor timing tasks similar to what is performed by their younger counterparts. However, for high-demand tasks that require processing beyond the level of available neural resources, the older brain can use compensatory mechanisms to ameliorate age-related decline in temporal processing of sensory stimuli during movement production. The findings showed that pre-motor ERP activities over the frontal areas were increased in older vs. younger adults when subjects produced speech movement in response to temporally unpredictable sensory stimuli. This age-related modulation of frontal ERPs during speech production may be a neural indicator of compensatory mechanisms for fronto-basal ganglia dysfunctions in older adults.

7.3 The Effects of Response Modality on Motor Reaction Times

Although studies in this dissertation suggest that speech and limb movement may share common temporal mechanisms, behavioral findings in this dissertation (see chapters 2, 4&5) showed that, regardless of stimulus timing, initiation and inhibition of limb movement were executed with shorter reaction times compared with speech. This finding can be explained by the inherent complexity of the speech motor task involving a
temporally-coordinated sequential activation of a large group of muscles (e.g. respiratory, laryngeal, articulatory, tongue and facial muscles) compared with button press. Consistent findings in previous studies support this idea by showing that complex movements require a longer processing time to be executed (Gajewski & Falkenstein, 2013, Ma & Trombly, 2004).

7.4 The Effect of Task on Motor Reaction Times

Despite the finding that initiation and inhibition of movement may be subserved by a common temporal mechanism, motor response time was significantly longer for movement initiation in both predictable and unpredictable conditions regardless of response modality. This effect can be explained by the fact that, in general, movement initiation is driven by a more complex mechanism that involves a motor program for sequential activation of a group of muscles with a specific timing pattern in order to reach the goals of the tasks during speech (producing the vowel sound) and limb movement (pressing a button). However, movement inhibition in our experimental task (stopping the vowel production or releasing the button) may have required a less complex mechanism because it does not involve a motor program for deactivating muscles to stop the ongoing motor action. Therefore, the observed effect associated with longer reaction time for movement initiation may be explained by the difference in complexity level of the mechanisms that drive movement initiation compared with inhibition. It is also noteworthy to mention that in our experiment, subjects were aware that they should be ready to start or stop movements in response to the onset of a specific cue; therefore, initiation and inhibition of movement shared the preparatory mechanisms that were required for activating (initiation) or deactivating (inhibition) muscle movements during
the tasks. Based on this notion, we suggest that the difference in reaction time between movement initiation and inhibition may be accounted for by the difference in programming and execution of motor commands, but not the planning of movements.

7.5. Conclusion and Future Directions

In summary, the findings of studies presented in this dissertation suggest that speech and limb movement may share common temporal predictive mechanisms to initiate/inhibit movement in response to sensory stimuli with predictable and unpredictable temporal pattern even though there are inherent differences and functional disassociation between these two modalities. In addition, findings indicate that pre-motor ERPs may be neural correlates of temporal predictive mechanisms in speech and limb motor systems. Finally, findings suggest that normal aging is associated with a selective decline in temporal predictive mechanisms during speech (but not hand movement) when the stimulus timing was unpredictable. In contrast, these mechanisms are relatively spared for speech and limb movement when stimulus timing was predictable. Overall, the findings of studies in this dissertation provide new insights into behavioral and neural correlates of temporal predictive mechanisms for speech and limb movement and highlight the age-related changes in these mechanisms in healthy older subjects.

Given the fact that ERPs do not provide adequate spatial resolution to identify the exact anatomical locations underlying brain function, future neuroimaging studies are warranted to investigate the neuroanatomical substrates of temporal predictive mechanisms for speech and limb movement in healthy young adults as well as in elderly
individuals. Finally, further studies in the future are required to provide new insights into the neural and behavioral correlates of temporal predictive mechanisms in neurological patients suffering from motor timing deficits such as those with Parkinson’s disease.

The findings of studies presented in this dissertation may have important clinical implications diagnosis and treatment of neurological patients with speech and limb movement disorders. Data from studies in this dissertation provide new insights into the behavioral and neurophysiological biomarkers that can be used to probe the integrity of temporal predictive mechanisms during the planning phase of the speech and limb movement. These biomarkers are critically important to identify the source of neural deficit in the motor system to guide targeted treatment of movement disorders using non-invasive brain stimulation technologies, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), to improve motor performance in neurotypical older adults or patients with neurological condition.
References


doi:10.1002/hbm.23012


doi:10.1016/j.pneurobio.2014.09.001


Merchant, H., Pérez, O., Bartolo, R., Méndez, J. C., Mendoza, G., Gámez, J., . . . Prado,
medial premotor cortex of the macaque. *European Journal of Neuroscience,*
41(5), 586-602.

Merchant, H., Pérez, O., Zarco, W., & Gámez, J. (2013). Interval tuning in the primate
medial premotor cortex as a general timing mechanism. *The Journal of
Neuroscience, 33*(21), 9082-9096.

*Neural networks, 9*(8), 1265-1279.

Whitford, T. J. (2016). Self-initiated actions result in suppressed auditory but
amplified visual evoked components in healthy participants. *Psychophysiology.*

Moberget, T., Karns, C. M., Deouell, L. Y., Lindgren, M., Knight, R. T., & Ivry, R. B.
(2008). Detecting violations of sensory expectancies following cerebellar
degeneration: a mismatch negativity study. *Neuropsychologia, 46*(10), 2569-
2579.


*Neural Netw, 9*(8), 1265-1279.


Appendix A Reprint Permission for Papers in Chapters 2&4  
(retireaved from Elsevier copyright center)

<table>
<thead>
<tr>
<th>Table ofAuthor’s Rights</th>
<th>Preprint version (with a few exceptions- see below *)</th>
<th>Accepted Author Manuscript</th>
<th>Published Journal Articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use for classroom teaching by author or author’s institution and presentation at a meeting or conference and distributing copies to attendees</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Use for internal training by author’s company</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Distribution to colleagues for their research use</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Use in a subsequent compilation of the author’s works</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Inclusion in a thesis or dissertation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reuse of portions or extracts from the article in other works</td>
<td>Yes</td>
<td>Yes with full acknowledgement of final article</td>
<td>Yes with full acknowledgement of final article</td>
</tr>
<tr>
<td>Preparation of derivative works (other than for commercial purposes)</td>
<td>Yes</td>
<td>Yes with full acknowledgement of final article</td>
<td>Yes with full acknowledgement of final article</td>
</tr>
<tr>
<td>Preprint servers</td>
<td>Yes</td>
<td>Yes with the specific written permission of Elsevier</td>
<td>No</td>
</tr>
<tr>
<td>Voluntary posting on open web sites operated by author or author’s institution for scholarly purposes</td>
<td>Yes (author may later add an appropriate bibliographic citation, indicating subsequent publication by Elsevier and journal title)</td>
<td>Yes, with appropriate bibliographic citation and a link to the article once published</td>
<td>Only with the specific written permission of Elsevier</td>
</tr>
<tr>
<td>Mandated deposit or deposit in or posting to subject-oriented or centralized repositories</td>
<td>Yes under specific agreement between Elsevier and the repository</td>
<td>Yes under specific agreement between Elsevier and the repository**</td>
<td>Yes under specific agreement between Elsevier and the repository**</td>
</tr>
<tr>
<td>Use or posting for commercial gain or to substitute for services provided directly by journal</td>
<td>Only with the specific written permission of Elsevier</td>
<td>Only with the specific written permission of Elsevier</td>
<td>Only with the specific written permission of Elsevier</td>
</tr>
</tbody>
</table>

** Voluntary posting of Accepted Author Manuscripts in the arXiv subject repository is permitted.
Appendix B
Reprint License for Paper in Chapter 3

SPRINGER NATURE LICENSE
TERMS AND CONDITIONS

This Agreement between Mr. Karim Joharikhatoonabad ("You") and Springer Nature ("Springer Nature") consists of your license details and the terms and conditions provided by Springer Nature and Copyright Clearance Center.

License Number 4546001225103
License date Mar 11, 2019
Licensed Content Publisher Springer Nature
Licensed Content Publication Experimental Brain Research
Licensed Content Title Premotor neural correlates of predictive motor timing for speech production and hand movement: evidence for a temporal predictive code in the motor system
Licensed Content Author Karim Johari, Roozbeh Behroozmand
Licensed Content Date Jan 1, 2017
Licensed Content Volume 235
Licensed Content Issue 5
Type of Use Thesis/Dissertation
Requestor type academic/university or research institute
Format electronic
Portion full article/chapter
Will you be translating? no
Circulation/distribution <501
Author of this Springer Nature content yes
Title dissertation
Institution name University of South Carolina
Expected presentation date Aug 2019
Appendix C
Reprint License for Paper in Chapter 5

SPRINGER NATURE LICENSE
TERMS AND CONDITIONS

This Agreement between Mr. Karim Joharikhatonabad ("You") and Springer Nature ("Springer Nature") consists of your license details and the terms and conditions provided by Springer Nature and Copyright Clearance Center.

<table>
<thead>
<tr>
<th>License Number</th>
<th>4546001102331</th>
</tr>
</thead>
<tbody>
<tr>
<td>License date</td>
<td>Mar 11, 2019</td>
</tr>
<tr>
<td>Licensed Content Publisher</td>
<td>Springer Nature</td>
</tr>
<tr>
<td>Licensed Content Publication</td>
<td>Aging Clinical and Experimental Research</td>
</tr>
<tr>
<td>Licensed Content Title</td>
<td>Effects of aging on temporal predictive mechanisms of speech and hand motor reaction time</td>
</tr>
<tr>
<td>Licensed Content Author</td>
<td>Karim Johari, Dirk-Bart den Ouden, Roozbeh Behroozmand</td>
</tr>
<tr>
<td>Licensed Content Date</td>
<td>Jan 1, 2018</td>
</tr>
<tr>
<td>Licensed Content Volume</td>
<td>30</td>
</tr>
<tr>
<td>Licensed Content Issue</td>
<td>10</td>
</tr>
<tr>
<td>Type of Use</td>
<td>Thesis/Dissertation</td>
</tr>
<tr>
<td>Requestor type</td>
<td>academic/university or research institute</td>
</tr>
<tr>
<td>Format</td>
<td>electronic</td>
</tr>
<tr>
<td>Portion</td>
<td>full article/chapter</td>
</tr>
<tr>
<td>Will you be translating?</td>
<td>no</td>
</tr>
<tr>
<td>Circulation/distribution</td>
<td>&lt;501</td>
</tr>
<tr>
<td>Author of this Springer Nature content</td>
<td>yes</td>
</tr>
<tr>
<td>Title</td>
<td>dissertation</td>
</tr>
<tr>
<td>Institution name</td>
<td>University of South Carolina</td>
</tr>
<tr>
<td>Expected presentation date</td>
<td>Aug 2019</td>
</tr>
</tbody>
</table>
Appendix D
Reprint License for Paper in Chapter

SPRINGER NATURE LICENSE
TERMS AND CONDITIONS

May 10, 2019

This Agreement between Mr. Karim Johari-Khatoonabad ("You") and Springer Nature ("Springer Nature") consists of your license details and the terms and conditions provided by Springer Nature and Copyright Clearance Center.

<table>
<thead>
<tr>
<th>License Number</th>
<th>4583840238813</th>
</tr>
</thead>
<tbody>
<tr>
<td>License date</td>
<td>May 07, 2019</td>
</tr>
<tr>
<td>Licensed Content Publisher</td>
<td>Springer Nature</td>
</tr>
<tr>
<td>Licensed Content Publication</td>
<td>Experimental Brain Research</td>
</tr>
<tr>
<td>Licensed Content Title</td>
<td>Behavioral and neural correlates of normal aging effects on motor preparatory mechanisms of speech production and limb movement</td>
</tr>
<tr>
<td>Licensed Content Author</td>
<td>Karim Johari, Dirk-Bart den Ouden, Roozbeh Behroozmand</td>
</tr>
<tr>
<td>Licensed Content Date</td>
<td>Jan 1, 2019</td>
</tr>
<tr>
<td>Type of Use</td>
<td>Thesis/Dissertation</td>
</tr>
<tr>
<td>Requestor type</td>
<td>academic/university or research institute</td>
</tr>
<tr>
<td>Format</td>
<td>electronic</td>
</tr>
<tr>
<td>Portion</td>
<td>full article/chapter</td>
</tr>
<tr>
<td>Will you be translating?</td>
<td>no</td>
</tr>
<tr>
<td>Circulation/distribution</td>
<td>&lt;501</td>
</tr>
<tr>
<td>Author of this Springer Nature content</td>
<td>yes</td>
</tr>
<tr>
<td>Title</td>
<td>dissertation</td>
</tr>
<tr>
<td>Institution name</td>
<td>University of South Carolina</td>
</tr>
<tr>
<td>Expected presentation date</td>
<td>Aug 2019</td>
</tr>
</tbody>
</table>