UNDERSTANDING CORTICAL ACTIVATION ASSOCIATED WITH SECOND LANGUAGE ACQUISITION

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To Mom and Dad

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) performed at a low frequency has been found to have an inhibitory effect on cortical function, which may result in behavioural consequences. Accordingly, rTMS may provide a valid model of focal cortical lesions, such as stroke, in healthy individuals. rTMS has been further proposed as a tool to inhibit high levels of cortical activity in individuals with aphasia in right hemisphere (RH) language homologues following a stroke that damages primary language regions. It is thought that while RH activity is compensatory during the early stages of recovery from stroke, it is maladaptive in terms of long-term recovery. RH activity has also been reported in healthy, low-proficiency bilinguals during second language (L2) production; thus, it has been proposed that RH activity may be better classified as reflecting effortful language production. Furthermore, given similarities in RH activity during language production in low-proficiency bilinguals and aphasics, non-disabled controls learning an L2 may provide a useful analogue to study aphasia.

The research presented in this dissertation examines learning of Spanish as an L2 in unilingual, English speaking adults in an attempt to understand which brain regions are associated with L2 acquisition, and the role that the RH plays in language functioning. Results of this project indicate that adults were able to learn novel Spanish vocabulary through a computer-based language-training program, but that learning was partially dependent on age and information processing capabilities. Unlike previous research that has demonstrated a more extensive network for L2 production, including regions of the RH, we found a less extensive network for Spanish than for English, although English language production was associated with RH activity. Furthermore, inhibitory rTMS produced no effects on lexical retrieval in either English or Spanish, indicating that the virtual lesion induced by TMS is not sufficient to mimic an aphasic stroke. Overall, our results indicate that while the RH does play an important role in language production, that role may differ between healthy and aphasic individuals. Also, neither L2 acquisition nor virtually induced lesions via TMS appear to provide an ideal model of post-stroke aphasia.

LIST OF ABBREVIATIONS AND SYMBOLS USED

□	IPA symbol for the voiced “th” sound
θ	IPA symbol for the voiceless “th” sound
ɲ	IPA symbol for the Spanish ñ
ʎ	IPA symbol for the Spanish ll
AoA	Age of arrival
BA	Brodmann area
BET	Brain extraction tool
cTBS	Continuous theta burst stimulation
DLPFC	Dorsolateral prefrontal cortex
ENG	English
FEAT	FMRI expert analysis tool
FLAME	FMRIB’s local analysis of mixed effects
fMRI	Functional magnetic resonance imaging
FMRIB	Functional MRI of the brain
FSL	Functional MRI of brain software tool
FWHM	Full width half maximum (Gausian kernel measurement)
GLM	General linear model
IFG	Inferior frontal gyrus
IPA	International phonetic alphabet
iTBS	Inhibitory theta burst stimulation
L2	Second language
LANGA	LANguage GAming

LH	Left hemisphere
M	Mean
MCFLIRT	FMRIB’s motion correction tool
MEP	Motor evoked potential
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
NBS	Noninvasive brain stimulation
PET	Positron emission tomography
RH	Right hemisphere
RMT	Resting motor threshold
ROI	Region of interest
rTMS	Repetitive transcranial magnetic stimulation
SD	Standard deviation
SMA	Supplementary motor area
SPN	Spanish
TBS	Theta burst stimulation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation

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CHAPTER 1 INTRODUCTION

1.1 OVERVIEW AND PURPOSE:

Repetitive transcranial magnetic stimulation (rTMS) performed at a low frequency has been proposed as a treatment for individuals with aphasia following a stroke (Barwood et al., 2011; Martin et al., 2004, 2009; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al., 2005; Naeser et al., 2010). However, the function of the brain regions which are the proposed targets of rTMS, which include regions of the right hemisphere (RH) believed to compensate for language deficits (Saur et al., 2006; Thiel et al., 2001; Winhuisen et al., 2005), are not well understood. Activation has been found in these regions both in individuals recovering from aphasia following stroke as well as in non-disabled individuals who are learning a second language (Raboyeau et al., 2008). Owing to the apparent similarity in activation patterns of RH brain regions between these two groups, non-disabled controls learning a second language may provide a useful analogue to patients with aphasia to examine brain activity patterns.

The purpose of this dissertation is to examine the role of RH language regions in second language (L2) acquisition in order to contribute to our understanding of and ultimately our ability to treat language disorders such as aphasia using rTMS. This thesis comprises three manuscripts, each highlighting a different aspect of this dissertation project, which used multiple research modalities to investigate the role of the RH of the brain in the early stages of L2 acquisition. This introductory chapter provides an overview of language organization in the brain during first and second language processing, followed by a discussion of the proposed similarities between RH involvement in recovery from aphasia and L2 learning. Subsequently, this chapter discusses the principles underlying TMS and the effects of TMS on language in healthy individuals, as well as its proposed use in the treatment of aphasia. This chapter concludes with a discussion of the overall goals and objectives of this dissertation and a brief introduction to each of the manuscripts included in this dissertation.

1.2 CORTICAL ORGANIZATION OF LANGUAGE

Language may be defined as the capacity that humans have for acquiring and using complex systems of communication involving words (Mesulam, 2000). The process of using language for communication involves an expressive and a receptive component, which includes auditory, comprehension, motor speech and other elements (Poldrack et al., 1999).

Much of what we know about language function in the brain comes from studies of neurological patients, such as individuals with aphasia following stroke, or epilepsy patients who have undergone intracarotid sodium amobarbital testing (Wada & Rasmussen, 1960) during pre-surgical evaluation to establish cerebral representation of language in each hemisphere. For example, damage to Broca's area, which is also defined as Broadmann area (BA) 44/45, and surrounding brain tissue may result in a condition known as Broca's aphasia. Broca's aphasia is characterized by phonological and lexical impairments that may include slow and labored speech, a lack of intonation, word finding difficulties, and difficulty distinguishing between phonemes, repeating words, or forming proper sentences despite an intact understanding of language (Mesulam, 2000). In contrast, damage to Wernicke's area, which includes left auditory association cortex (BA22) and surrounding tissue may result in fluent aphasia, which is characterized by effortless and melodic speech, but with semantic and/or phonemic paraphasias, in which words or phonemes may be erroneously substituted during speech, as well as difficulty comprehending spoken language (Mesulam, 2000). Accordingly, the two epicenters of a more widely distributed language network are traditionally understood to be Broca's and Wernicke's areas in the left hemisphere (LH; Mesulam, 2000).

However, recent developments in non-invasive functional brain imaging have advanced our understanding of the complex network of cortical and subcortical regions involved in language processing in healthy individuals (Mesulam, 2000; Vigneau et al., 2006). It has been suggested that there are three primary components of language: phonological, semantic, and syntactical (Bookheimer, 2002; Mesulam, 2000; Vigneau et al., 2006), which are processed primarily in LH language regions. Phonological processing involves distinguishing between speech sounds, semantic processing involves connecting words with their meaning, and syntactical processing refers to an understanding of the rules and principles that govern sentence structure (Bookheimer, 2002; Vigneau et al., 2006). Although there has been some debate over the specific cortical regions responsible for these components of language, and whether processing of these components occurs in separate or overlapping cortical regions, neuroimaging research supports the existence of separate, but highly connected subsystems that are distributed widely throughout cortical areas in the frontal, temporal, and parietal lobes (See Bookheimer, 2002; Vigneau et al., 2006 for reviews).

In an analysis of activation for phonological and semantic processing tasks that involved case judgment (upper or lower case), category judgment (abstract or concrete), and syllable counting for words and pseudowords, Poldrack et al. (1999) proposed a functional differentiation for the inferior frontal gyrus (IFG): The anterior/ventral extent, including the pars triangularis and orbitalis, for semantic processing, and the posterior/dorsal IFG, including the pars opercularis, for both semantic and phonological processing. These findings were refined further in a meta analysis by Vigneau et al. (2006) that analyzed peak activations reported in the literature for phonological, semantic, and sentence processing, and revealed additional activation clusters specific to phonological and semantic as well as syntactical processing.

Based on the results of their meta analysis, Vigneau et al. (2006), proposed two main neural components of phonological processing networks. The first, a frontal-temporal pathway that governs auditory-motor speech coordination, consists of frontal lobe regions that control mouth, pharynx, and tongue movement, as well as a sensory-motor integration region in the Rolandic operculum, which are linked via the arcuate fasciculus to the posterior superior temporal gyrus, which appears specialized for phonological processing during auditory tasks. The second, a frontal-parietal phonological working memory network, includes the dorsal portion of the pars triangularis and parts of the supramarginal gyrus, also connected by the arcuate fasciculus; this network provides neural evidence of the phonological working memory loop proposed by Baddeley (2003). In contrast to Poldrack et al. (1999), who reported no specialized region for phonological processing specifically, Vigneau et al. (2006) suggest that the dorsal portion of the pars triangularis contains regions that are more active for phonological processing, whereas the ventral pars triangularis is more active for semantic processing.

Other regions that appear to be specialized for processing of semantic information include the pars opercularis and the pars orbitalis, which have been implicated in controlled semantic retrieval (Bookheimer, 2002; Vigneau et al., 2006; A. D. Wagner, Paré-Blagoev, Clark, & Poldrack, 2001). These frontal regions form part of a frontal-temporal semantic network, which connects along a dorsal route through the angular gyrus, which is involved in conceptual knowledge (Mesulam, 2000), and the anterior fusiform gyrus, which is involved in semantic processing of words and pictures (Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996), to the temporal pole through the arcuate fasciculus; and from the temporal pole to the orbital frontal cortex through the uncinate fasciculus (Catani, Howard, Pajevic, & Jones, 2002; Vigneau et al., 2006). The pars opercularis is also connected along a ventral route to the superior temporal gyrus, which may be involved in auditory processing to make semantic information accessible in verbal format for further processing (Vigneau et al., 2006).

Although less germane to the specific goals of this dissertation project, briefly, syntactical processing appears to be governed partly by areas in the dorsal pars opercularis and ventral pars triangularis, which overlap with semantic processing (Bookheimer, 2002; Vigneau et al., 2006). However, the temporal lobe in particular appears to play a key role in syntactical processing, sentence comprehension, and integration of complex linguistic materials (Vigneau et al., 2006). The neuroanatomy of language processing is a vast and complex topic, and has been covered in more detail in several excellent reviews (Bookheimer, 2002; Hickok & Poeppel, 2000, 2004; Vigneau et al., 2006).

1.3 THE ROLE OF THE RIGHT HEMISPHERE IN LANGUAGE PROCESSING

In terms of phonological, semantic, and syntactical processing of language, there is evidence that RH activity is not specific to any particular language function. For example, in a recent meta analysis Vigneau et al. (2011) reported that activity in the pars opercularis of the RH occurred during tasks related to all three language components, and this region was frequently activated together with the anterior insula. This was interpreted as representing executive functions that are not specific to any particular language process. For example, the pars opercularis may support the manipulation of both phonological representations and complex verbal material in working memory, however it does not appear that the RH specifically hosts phonological or semantic representation of language. Likewise, the anterior insula may support auditory attention and the manipulation of complex verbal, spatial, and numerical information in working memory rather than any specific language-based function (Vigneau et al., 2011).

In addition to the three components of language described above, which are strongly left lateralized, a fourth component of language, prosody, which is governed primarily by the RH has been proposed. Prosody consists of pitch, rhythm, and syllable stress that create melodic intonation of speech and allow humans to differentiate statements from questions, and communicate subtleties such as sarcasm or emotional state (Ross & Mesulam, 1979). Several neuropsychological studies of emotional communication have demonstrated that the RH plays an important role both in the decoding and encoding of prosody in speech (Beaucousin et al., 2007; Blonder, Bowers, & Heilman, 1991; Buchanan et al., 2000; Ross & Mesulam, 1979; Ross & Monnot, 2008).

Specifically, Ross and Monnot (2008) demonstrated that expression of affective prosody is governed by right inferior frontal regions and comprehension of affective prosody is governed by right temporal regions, including Heschl's gyrus. This is consistent with previous findings of deficits in either expressive or receptive emotional prosody following RH damage. For example, Ross and Mesulam (1979) reported two cases of patients who had suffered the loss of prosody and emotional gesturing following infarctions to right frontal and anterior parietal regions. In both cases, vocabulary, grammar and articulation were intact; and despite an intact ability to experience emotion and interpret prosody and emotion in others, both patients demonstrated a flat affect with monotone speech and were unable to match the tone of their voices to the emotion that they wished to convey. Conversely, Blonder et al. (1991)

reported that relative to normal controls or patients with LH damage, patients with RH damage (often including right temporal regions) were unable to discriminate intonation, facial expressions of emotion, or the emotion conveyed by verbal prosody. Finding that damage to RH language regions impairs either the expression or comprehension of emotional prosody have been interpreted to mean that the prosodic component of language is a dominant function of the RH (Ross & Mesulam, 1979; Ross & Monnot, 2008).

It has also been suggested that the RH plays an important role in integrating semantic information into context, which involves judgment or decision making about linguistic information to construct meaning and intent (See Bookheimer, 2002; Lindell, 2006 for reviews). This may include the ability to understand non-literal expressions, such as idioms, proverbs, or slang (Sidtis, 2009). For example, the anterior frontal lobe of the RH has been implicated in the ability to understand and appreciate humour, which often involves understanding the context in which a joke is presented. Marinkovic et al. (2011) found that funny joke endings resulted in stronger activity in the right dorsolateral prefrontal cortex (DLPFC) relative to neutral or incongruous joke endings, indicating that the right DLPFC has a unique sensitivity to funny punch lines. Similarly, stroke patients with RH anterior frontal lesions were impaired in their ability to appreciate humour, complete a joke by choosing an appropriate ending to a joke stem, or distinguish between humorous and neutral non-verbal cartoons compared to patients with lesions in the LH or right posterior lesions (Shammi & Stuss, 1999).

1.4 RIGHT HEMISPHERE INVOLVEMENT IN STROKE RECOVERY

Although there is consistent evidence that the right inferior frontal cortex plays a limited role in phonological, semantic, and syntactical language processing, there is evidence of unusually high levels of cortical activation in RH language homologues such as the right counterpart of Broca's area (Karbe, Thiel, et al., 1998; Thiel et al., 2001; Weiller et al., 1995), bilateral supplementary motor areas (SMA; Karbe, Thiel, Weber-luxenburger, Kessler, & Heiss, 1998), and the insular cortex (Raboyeau et al., 2008) in the subacute stage of post-stroke aphasia. It has been hypothesized that in partially recovered aphasics, RH opercular regions can support speech production (Blank, Bird, Turkheimer, & Wise, 2003; Hartwigsen et al., 2013), and RH inferior frontal cortex supports word retrieval from long-term memory (Blasi et al., 2002) when a stroke has damaged LH language regions. However, it is thought that such compensation is maladaptive to recovery in the long term (Belin et al., 1996; Karbe, Thiel, et al., 1998; Martin et al., 2004; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al., 2005; Rosen et al., 2000).

Although the mechanism behind the left-right hemisphere shift in activation following damage to LH language regions has not been clearly identified, one possible explanation relies on the theory of interhemispheric competition (Fregni & Pascual-Leone, 2007; Mesulam, 1999). It is hypothesized that typically, normally functioning language regions in the LH inhibit RH activity during language tasks; this phenomenon is known as transcallosal inhibition (Netz, 1995, 1999). In line with the theory of interhemispheric competition, activation of RH language homologues following a LH lesion is interpreted as being caused by reduced transcallosal inhibition, or a release of RH frontal activity (Price & Crinion, 2005; Thiel, Schumacher, et al., 2006; Thulborn, Carpenter, & Just, 1999). An alternate explanation for increased RH activity following LH stroke is the functional recruitment hypothesis. This hypothesis suggests that undamaged RH regions, which are functionally connected to the speech network but not normally needed for language processing, are recruited through an inter-hemispheric shift in language networks in order to cope with aphasic impairment (Musso et al., 1999; Rosen et al., 2000; Saur et al., 2006). Regardless of the mechanism behind the left-right hemisphere shift in activation, chronic activation of RH regions without recovery of LH language functioning is thought to be a maladaptive process indicative of poor recovery (Belin et al., 1996; Martin et al., 2004; Naeser et al., 2004; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al., 2005; Rosen et al., 2000).

1.5 CORTICAL ACTIVITY ASSOCIATED WITH SECOND LANGUAGE LEARNING

The extent of cortical activation associated with L2 processing is a contentious and highly debated topic within the literature. Whereas some researchers have argued that distinct cortical representations exist for first (L1) and L2 processing (e.g. Kim, Relkin, Lee, & Hirsch, 1997; Raboyeau et al., 2004), others have argued for a shared representational system for L1 and L2 (e.g. Green, 2003; Klein, Milner, Zatorre, Zhao, & Nikelski, 1999). To date, the majority of research has supported that L1 and L2 are processed by a common neural circuitry (See Abutalebi & Chang-Smith, 2013 and Indefrey, 2006 for reviews). Several studies have provided neuroimaging evidence of a shared neural substrate that is active for both L1 and L2 processing during expressive (Chee, Tan, & Thiel, 1999; Klein et al., 1999; Liu, Hu, Guo, & Peng, 2010) and receptive (Chee, Caplan, et al., 1999; Klein, Zatorre, et al., 2006) language tasks.

However, there is also evidence of spatially segregated regions of peak activation during language processing in L1 compared to L2 (K. H. Kim et al., 1997), which has been interpreted as evidence of distinct cortical regions that are language specific within the larger language network (Abutalebi & Green, 2008). Indeed, a number of researchers have reported finding a more widely distributed language network during L2 processing in bilateral frontal regions in high proficiency early bilinguals during phonemic fluency (Perani et al., 2003), in high proficiency late bilinguals during lexical decision tasks (H. R. P. Park, Badzakova-Trajkov, & Waldie, 2012), and in low proficiency late bilinguals during semantic judgment (Wartenburger et al., 2003) and syntactical processing (Golestani et al., 2006) relative to L1. Furthermore, other researchers have found evidence of activation in RH homologues of LH language areas (i.e., inferior frontal gyrus and insular cortex) during word retrieval tasks in non-disabled control participants who were asked to learn a second language (Raboyeau et al., 2004, 2008).

More extensive activation during L2 than L1 processing has been explained in terms of additional cognitive control required for more effortful language processing (Green, 1986; Rudner & Rönnberg, 2008). It has been suggested that both articulation (Raboyeau et al., 2008), and lexical retrieval (Green, 1986; Rudner

& Rönnberg, 2008) of recently acquired or less familiar L2 vocabulary is more effortful than L1 processing, which is relatively automatic. Thus, effortful lexical retrieval owing to phonological and semantic limitations in an L2 may require additional attentional and working memory resources during language processing (Perani et al., 2003; Raboyeau, Marcotte, Adrover-Roig, & Ansaldo, 2010; Rudner & Rönnberg, 2008), which may result in increased activity in regions of the prefrontal cortex (Briellmann et al., 2004; De Bleser et al., 2003; Green, 1986; Perani et al., 2003).

More extensive cortical activity during L2 processing may be particularly evident during the very early stages of L2 acquisition, and in very low proficiency L2 learners, as RH language homologues may be recruited during effortful lexical retrieval (Raboyeau et al., 2004, 2008). For example, during a picture-naming task, individuals with very low L2 proficiency activated an extensive RH network including frontal, temporal, subcortical, and cerebellar regions when naming pictures in their L2 compared to their native language (Raboyeau et al., 2004). Furthermore, a comparison of right inferior frontal activity in low proficiency L2 learners and in aphasic patients following a lexical training program revealed a similar pattern of activity in right frontal and insular regions induced by improved lexical retrieval (Raboyeau et al., 2008). Accordingly, and in line with the functional recruitment hypothesis, the authors concluded that enhanced RH activity both in recovering aphasics and L2 learners may reflect compensatory activity in RH language homologues related to effortful lexical retrieval and articulatory processing. Moreover, the authors proposed that lexical difficulties associated with accessing the phonologic forms of foreign names for objects in the poorly developed L2 lexicon creates an “anomia-like situation” which may parallel the word finding difficulties observed in mild aphasia (Raboyeau et al., 2008, p. 295). Thus, very low proficiency during early L2 acquistion may provide a model of effortful language production in terms of both lexical retrieval and articulatory processing. This effortful language production may resemble that which occurs in Broca’s aphasia following damage to LH language regions.

However, while it is clear that the RH plays an important role in recovery from aphasia, it is unclear what specific role RH language homologues may play during the effortful phonetic and semantic processing associated with learning an L2. More specifically, there remains some debate as to whether abnormal levels of RH activity associated with L2 production represent an extension of existing language circuitry combined with additional cognitive processes such as attention and verbal working memory, which have been shown to be more right lateralized in older than younger individuals (Reuter-Lorenz et al., 2000), or maladaptive functional recruitment, similar to that which may occur following a LH lesion (Raboyeau et al., 2008).

1.6 TRANSCRANIAL MAGNETIC STIMULATION (TMS)

Transcranial magnetic stimulation (TMS) is a noninvasive and relatively painless procedure that has been used in a growing number of laboratories worldwide since 1985 for both experimental and clinical purposes. TMS involves using a series of brief magnetic pulses applied on the outside of the head over cortical regions of the brain to excite cortical tissue. Briefly, TMS relies on the properties of electromagnetic induction; a rapidly changing magnetic field is generated when a high-voltage current is passed through a coil. When this coil is held in close proximity to any electrically conducting medium, such as the brain, this time-varying magnetic field induces current in a direction opposite to the original current in the coil (Bolognini & Ro, 2010; Hallett, 2000). TMS can be applied one stimulus at a time (single-pulse TMS), in pairs of stimuli separated by a variable interval (paired-pulse TMS), or in trains (rTMS). Single-pulse TMS can be used, for example, for mapping motor cortical outputs, studying central motor conduction time, and studying causal chronometry in brain-behavior relations. In paired pulse techniques TMS can be delivered to a single cortical target using the same coil, or to two different brain regions using two different coils. Paired pulse techniques can provide measures of intracortical facilitation and inhibition, and can be used to study cortico–cortical interactions (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). rTMS can be used to transiently facilitate (excite) or disrupt (inhibit) neural activity, with the desired outcome (facilitation or disruption) achieved based on the frequency of stimulation used (Rossi et al., 2009). The basic principles of TMS have been covered in more detail in many excellent reviews (i.e. Bestmann et al., 2008; Pascual-Leone, Walsh, & Rothwell, 2000; Ziemann et al., 2008).

As highlighted above, rTMS performed at low frequencies (≤ 1 Hz; ‘inhibitory rTMS’) can be used to temporarily disrupt the function of a specific cortical region, thus creating a ‘virtual brain lesion’ (Pascual-Leone, Bartres-Faz, & Keenan, 1999). rTMS has been found to result in transient neural processes (Allen, Pasley, Duong, &

Freeman, 2007; Levkovitz, Marx, Grisaru, & Segal, 1999) and hemodynamic changes (Allen et al., 2007) that correspond to the duration and frequency of stimulation. For example, effects typically last 15-30 minutes following approximately 20 minutes of stimulation at frequencies lower than 1 Hz (W. H. Chen et al., 2003). The ability to transiently disrupt the activity of a given brain region in this manner makes it possible to study the contribution of a specific region to a given behavioural outcome.

Theta Burst Stimulation (TBS) is a form of rTMS in which magnetic pulses are applied in bursts of three, 50Hz pulses, delivered at intervals of 200ms. In continuous TBS (cTBS), 50Hz pulses are applied in bursts of three at a frequency of 5Hz. Continuous TBS protocols that have applied these bursts over a period of 40 seconds (200 bursts), have resulted in cortical inhibition (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). TBS has been used in an increasing number of laboratories since 2004 (e.g. Hartwigsen et al., 2013; Kindler et al., 2012) as this protocol uses fewer pulses and a much shorter duration of stimulation than typical low-frequency rTMS paradigms (Oberman, Edwards, Eldaief, & Pascual-Leone, 2011). Specifically, one session of TBS lasts only approximately 40 seconds, compared to a typical 20-minute session using rTMS performed at low frequency. A shorter duration of stimulation is not only more convenient for participants, but also results in a lesser degree of potential discomfort due to uninterrupted stimulation applied to the head for an extended period of time, which may place unnecessary strain on the muscles of the head and neck (Huang & Rothwell, 2010). Also, the effects of TBS have been found to last for 60 minutes after only 40 seconds of TBS; more than twice as long as the effects following 20 minutes of typical rTMS (Huang et al., 2005; Huang, Rothwell, Chen, Lu, & Chuang, 2011).

Based on a number of TBS studies carried out between 2004 and 2009, TBS has been found to carry a general risk that is comparable to other high frequency rTMS protocols (Oberman et al., 2011). Additionally, several studies have been completed using TBS in both control and patient populations between 2009 and 2012 with no reported incidence of adverse events, pain, or other side effects (Kindler et al., 2012; Nardone et al., 2011; Restle, Murakami, & Ziemann, 2012).

1.7 EFFECTS OF TMS ON LANGUAGE PROCESSING

1.7.1 TMS AND NON-APHASICS

Early TMS studies have reported TMS induced speech disruption or arrest in patients with epilepsy following brief sessions of rTMS over regions of the LH corresponding to Broca's area (Jennum, Friberg, Fuglsang-Frederiksen, & Dam, 1994; Pascual-Leone, Gates, & Dhuna, 1991; Wassermann et al., 1999). These reports are consistent with those of impaired picture naming during invasive electrical stimulation during brain surgery (Black & Ronner, 1987; Ojemann & Whitaker, 1978; Ojemann, 1983; Penfield & Rasmussen, 1949). More recently, research has demonstrated that TMS is effective in modulating language functioning in healthy controls. Inhibitory rTMS over the anterior portion of Broca's area (BA45) has been found to interfere with speed of processing during a semantic decision task (Devlin, Matthews, & Rushworth, 2003; Köhler, Paus, Buckner, & Milner, 2004) and rTMS over the posterior portion of Broca's area (BA44) had an adverse affect on phonological working memory (Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004) and speed of phonological processing (Aziz-Zadeh, Cattaneo, Rochat, & Rizzolatti, 2005). Furthermore, inhibitory TMS over the left IFG in healthy control subjects has been found to result in increased reaction time latencies and abnormal right IFG activity during a verb generation task (Thiel et al., 2006). Based on evidence that rTMS may interfere with cortical activity associated with language processing, it has been suggested that TMS over LH cortical language regions provides a valid model of focal cortical lesions, and may therefore mimic the effects of an aphasic stroke (Andoh & Martinot, 2008; Knecht et al., 2002).

1.7.2 TMS IN THE TREATMENT OF APHASIA

As reviewed above, a left-right hemisphere shift in language-related activity following a LH lesion may assist recovery of speech initially, however, chronic activation in RH language homologues is thought to be a maladaptive process indicative of poor recovery (Belin et al., 1996; Martin et al., 2004; Naeser et al., 2004; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al., 2005; Rosen et al., 2000). For example, activation of the right SMA in the chronic stage of aphasia has been associated with persisting language deficits, whereas recovery of left perilesional regions in the superior temporal cortex was associated with recovery of language function, and decreased RH activity (Karbe, Thiel, et al., 1998). Several studies have likewise reported that reintegration and recruitment of left perilesional areas in the frontal and temporal lobes is associated with better overall recovery from aphasia (Cao, Vikingstad, George, Johnson, & Welch, 1999; Heiss, Kessler, Karbe, Fink, & Pawlik, 1993; Karbe, Thiel, et al., 1998; Miura et al., 1999; Weiller et al., 1995). Thus, it is hypothesized that the use of inhibitory rTMS to suppress RH language homologues that are presumed overactive on the basis of observed high blood flow during fMRI tasks may serve to temporarily constrain compensatory activity in these regions. This in turn may result in improved language function, through paradoxical functional facilitation of perilesional cortex in or adjacent to primary LH language regions (Crinion & Leff, 2007; Daskalakis, Christensen, Fitzgerald, & Chen, 2002; Hartwigsen et al., 2013; Kakuda, Abo, Kaito, et al., 2010; Martin et al., 2004, 2009; Naeser et al., 2010; Schnitzler, Kessler, & Benecke, 1996).

Indeed, research has provided evidence for the use of rTMS to treat individuals with chronic aphasia who have experienced a stroke that has damaged normal left hemisphere language regions (Barwood et al., 2011; Kakuda, Abo, Kaito, et al., 2010; Kakuda, Abo, Uruma, Kaito, & Watanabe, 2010; Martin et al., 2004, 2009; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al., 2005; Naeser et al., 2010). For example, in a cohort of individuals with chronic aphasia, individuals who received 10, 20-minute sessions of 1Hz rTMS administered to the right pars triangularis demonstrated significant improvements in picture naming, spontaneous speech, and auditory comprehension (Barwood et al., 2011) compared to a sham TMS group. Furthermore, after a similar TMS protocol, with each session of TMS followed by 45 minutes of speech and language therapy (SLT), patients with various types of aphasia demonstrated both improvements on a measure of aphasia severity as well as changes in functional brain activity compared to a control group who received sham TMS. Specifically, greater increases in LH activation pre- to post-TMS were associated with greater improvement in language functioning following treatment with TMS and SLT combined (Thiel et al., 2013).

Within Broca's area, research has indicated that the dorsal part of BA44 is involved in phonological processing, whereas BA45 and the ventral portion of BA44 are involved in semantic processing (Poldrack et al., 1999; Vigneau et al., 2006). To date, nearly all studies that have supported the use of rTMS as treatment for aphasia, including both Broca's and Wernicke's aphasia, have involved administration of TMS to the right pars triangularis (BA45) of the inferior frontal gyrus (IFG), which is homologous to semantic processing cortex in the LH (Barwood et al., 2011; Hamilton et al., 2010; Martin et al., 2009; Naeser et al., 2010; Thiel et al., 2013) – a region homologous to the portion of Broca's area that has been shown to be involved in semantic processing (Abutalebi, Cappa, & Perani, 2001; Binder, Desai, Graves, & Conant, 2009). Using an approach that involved stimulating various regions of the right IFG to determine the most effective target for TMS, Naeser et al. (2010) determined that the pars triangularis, but not other right hemisphere targets resulted in the best response to TMS (i.e. improved picture naming). In contrast, they reported that inhibition of the pars opercularis (BA44), the homologue of the part of Broca's area associated with motor speech and phonological processing (Heim & Friederici, 2003), often transiently impaired picture naming (Naeser et al., 2002, 2010).

1.8 OVERARCHING GOALS OF THE CURRENT RESEARCH

This dissertation aims to further our understanding of the role of the right hemisphere in effortful phonetic processing of a second language. The overarching goal of this research is to add to our understanding of language learning circuitry and provide the basis for further research on treatment of language disorders such as aphasia.

The specific goals of this dissertation project were threefold. First, teach participants Spanish vocabulary using a computer-based language-training program, with the goal of treating effortful lexical retrieval and articulation of newly acquired L2 vocabulary as a proxy for the word finding difficulties seen in Broca's aphasia. Second, determine what cortical regions are differentially active during verbal naming tasks when individuals are in the early stages of learning an L2 as compared to verbal naming tasks completed in their native language. Third, determine the effect of inhibitory cTBS applied to regions with activation specific to L2 picture naming on both language learning and speech production in Spanish, and on speech production in English.

We hypothesize that participants will be able to learn Spanish vocabulary through a computer-based language-training program. However, given the additional articulatory effort associated with pronouncing recently acquired words in a new language (Abutalebi & Green, 2008; Raboyeau et al., 2008), we expect that on average, both recall and pronunciation of novel Spanish words will be imperfect, reflecting effortful lexical retrieval and articulation. Secondly, based on previous research that has found cortical activation in the right inferior frontal gyrus and insular cortex in adults learning a second language (Raboyeau et al., 2008), we hypothesize that in addition to areas that are normally involved in speech production (Vigneau et al., 2006), participants in our study will also show cortical activation in right hemisphere language homologues during Spanish naming tasks. Thirdly, based on findings that TMS over the right pars opercularis transiently impaired picture naming in aphasics (Naeser et al., 2002, 2010), we hypothesize that participants who receive cTBS to right hemisphere language regions will show a decline in Spanish naming performance. Conversely, based on previous findings that TMS over LH language regions interfered with speed of processing for semantic and phonological information (Aziz-Zadeh et al., 2005; Devlin et al., 2003; Thiel, Schumacher, et al., 2006), combined with the suggestion that inhibitory TMS over LH cortical language regions may mimic the effects of an aphasic stroke through a virtual cortical lesion (Andoh & Martinot, 2008; Knecht et al., 2002), we hypothesize that participants who receive cTBS to left hemisphere language regions will show a decline in English naming performance. Finally, based on findings that inhibitory rTMS over Broca's homologue combined with SLT resulted in improved language outcomes, we anticipate that cTBS over RH language regions will facilitate further Spanish learning.

1.9 OVERVIEW OF CURRENT MANUSCRIPTS

This thesis is composed of three manuscripts, each highlighting a different aspect of the dissertation project:

1.9.1 AGE AND SPEED OF INFORMATION PROCESSING PREDICT COMPUTER-BASED VOCABULARY LEARNING OF A SECOND LANGUAGE IN UNILINGUAL ADULTS

In this manuscript we evaluated the capacity for initial L2 vocabulary acquisition in unilingual adults using computer-based language-training software called LANGA (LANguage GAming). In this portion of the study participants were asked to complete two training sessions followed by a test of vocabulary acquisition. A multiple regression analysis was used to investigate the contribution of factors such as age, level of education, and cognitive abilities to L2 learning.

1.9.2 CORTICAL REGIONS ACTIVE DURING PICTURE NAMING IN THE EARLIEST STAGES OF SECOND LANGUAGE ACQUISITION

Given reports of similar RH brain activity in low-proficiency bilinguals and individuals with aphasia during speech production (Raboyeau et al., 2008, 2010), this portion of the dissertation project used fMRI to investigate cerebral language organization in healthy controls who were in the early stages of L2 learning during picture naming in English (L1) and in Spanish (L2). The objective of this study was to determine whether early L2 learning results in a similar pattern of activity as that reported in previous research, and whether cortical activity associated with L2 acquisition may provide a model of the effortful lexical retrieval and articulation associated with Broca's aphasia.

1.9.3 WHAT ARE THE EFFECTS OF cTBS OVER BROCA'S AREA AND BROCA'S HOMOLOGUE ON LANGUAGE LEARNING AND PRODUCTION?

The objective of this final portion of the dissertation project was to investigate the effects of inhibitory TMS over cortical areas associated with language production. It has been suggested that virtual lesions induced in primary language regions through TMS may mimic the effects of an aphasic stroke (Andoh & Martinot, 2008; Knecht et al., 2002). Previous research has also found that inhibitory TMS over RH language homologues may facilitate speech production in aphasics (Naeser et al., 2010). Thus, this study was conducted to investigate the effects of TMS over Broca's area in the LH vs. Broca's homologue in the RH on language production in both native English and newly acquired Spanish.

CHAPTER 2 AGE AND SPEED OF INFORMATION PROCESSING PREDICT COMPUTER-BASED VOCABULARY LEARNING OF A SECOND LANGUAGE IN UNILINGUAL ADULTS

2.1 ABSTRACT

This study examined the effect of using speech recognition-based video games to teach vocabulary in a new language. LANGA (LANguage GAming); a novel, computer-based approach to second language instruction relies on acoustic-visual word pairings and speech recognition software combined with video games to teach new vocabulary and shape learning through feedback. Learners were asked to play a series of language games in which they had to respond verbally to pictures of objects with newly learned vocabulary items in order to complete tasks within each game. On average, participants were able to learn 18.32 items in the new language, out of a total of 48 word-item pairings trained over a two-day training period. Language learning, defined as the number of items correctly named in the new language at the end of training, was negatively correlated with age and positively correlated with speed of information processing. Recommendations for future development of computer-based language software are provided.

2.2 INTRODUCTION

2.2.1 CONSIDERATIONS IN SECOND LANGUAGE-TRAINING

With the spread of globalization, second and foreign language education has attracted increasing interest. Millions of people voluntarily attempt to learn a second language (L2) each year for personal, professional, immigration, religious, or other reasons (Long, 2009). Increasingly, foreign languages are taught to children in schools and multilingualism is being recognized as important in many global or international organizations and national governments (Long, 2009). There is also emerging evidence that bilingualism may support cognitive functioning in healthy aging and postpone the onset of symptoms of dementia (Bialystok, Craik, & Freedman, 2007; Bialystok, Craik, & Luk, 2012; Craik, Bialystok, & Freedman, 2010). However, the issue of how second language (L2) training should be delivered has been widely debated in second language acquisition (SLA) research since the 1980s. A number of theories of L2 learning have been put forth, beginning with the behaviorist tradition of deliberate paired-associate learning (Skinner, 1957), in which repeated practice is used to drive learning; and followed by communicative teaching approaches, in which language is learned implicitly through contextual learning (See Dixon et al., 2012; Elgort, 2011; and Mori, 2007 for reviews). However, there is mounting evidence that deliberate learning, in which the learner is aware that the primary goal of an activity is to form an intentional linkage between previously learned and new information, is more effective than incidental learning in the acquisition of novel vocabulary (Elgort, 2011; Hulstijn & Laufer, 2001; Hulstijn, 2005; Laufer & Rozovski-Roitblat, 2011; Laufer-Dvorkin, 2006; Peters & Hulstijn, 2009; Peters, 2012). This has prompted a return to deliberate approaches to L2 training.

With respect to foreign vocabulary learning, recent literature comparing the efficacy of message-oriented learning, in which passages of text contain target words that learners must look up on their own initiative, and vocabulary-based learning, in which learners are provided with explicit definitions of target words, has demonstrated that explicit, vocabulary-based activities are more effective than implicit, message-oriented activities for teaching novel vocabulary (Hulstijn & Laufer, 2001; Laufer & Rozovski-Roitblat, 2011; Laufer-Dvorkin, 2006; Peters & Hulstijn, 2009; Peters, 2012). For example, Grace (2000) found that learners who were provided with L1 translations of target words and sentences while reading scored higher on both short- and long-term vocabulary recognition tests than learners who completed an identical learning task but did not have translations provided. Likewise, students who were enrolled in an L2 university course were randomly assigned to read a passage of text that contained 14 target words followed by either a message-oriented learning task, which involved comprehension questions that were answered in the learners' L1, or a vocabulary-oriented learning task, which involved direct translation of target words and a multiple choice task in which learners had to identify the correct meaning of the target word. Results indicated that students in the vocabulary-oriented condition, who had processed the meaning of target words explicitly, had higher recall and retention on direct translation and multiple choice vocabulary tests (Peters, 2012). However, in the study by Peters (2012), although the post-tests were not identical to the training tasks in the vocabulary-oriented condition, the training and testing conditions were much more similar in the vocabulary-oriented than the message-oriented condition, introducing a potential systematic bias in favor of the explicit learning task.

Laufer and Rozovski-Roitblat (2011) studied vocabulary learning in 20 university students with intermediate pre-training L2 ability who completed a 13-

week L2 training program. Learners were exposed to 60 target words: 30 presented in an implicit learning context, and 30 in an explicit learning context. In the implicit learning context, students were required to look up the meaning of target words in a dictionary. The explicit learning context required students to practice using the target words in different contexts and in sentences. Target words were matched for difficulty and linguistic features across conditions, and learning was tested through explicit recall, in which students were asked to provide a definition of the target words, and recognition of multiple-choice items. Results indicated that when target words were presented four or more times during training, students were able to define more of the target words in the explicit than the implicit condition.

Taken together, the results reviewed above (Grace, 2000; Laufer & Rozovski-Roitblat, 2011; Peters, 2012) indicate that explicit vocabulary training, which forces a deeper processing of word meaning through direct translation of new L2 words combined with context-based usage, is more effective for building lexical knowledge than implicit training programs that do not involve a deep, contextual processing component.

2.2.2 LEXICAL LEARNING IN MONOLINGUAL ADULTS

However, to date, the majority of studies have investigated L2 learners with previous exposure to the target language (Abrahamsson & Hyltenstam, 2009; Birdsong & Molis, 2001; Peters & Hulstijn, 2009; Peters, 2012), rather than adults with no prior L2 training. Although we are not aware of any studies that have examined the capacity for L2 vocabulary acquisition in unilingual adults with no previous L2 exposure, there have been some studies in which pseudowords have been taught to monolingual adults. An advantage of using pseudowords to investigate vocabulary acquisition is that participants are guaranteed to have no prior exposure to the words being taught, thus it is possible that the capacity of monolingual adults to learn auditorily presented pseudowords may parallel the initial stages of vocabulary learning in an L2.

Breitenstein and Knecht (2002) developed a set of 50, two-syllable pseudowords containing four letters each that were not consistently associated with real words by participants, that had neutral emotional valence, and that 80% of participants were able to write correctly. They also chose 50 drawings from the from the Snodgrass and Vanderwart (1980) picture set that were paired with the pseudowords. Subsequent studies trained participants using an implicit pseudoword-picture association protocol, in which 45 correct and incorrect pairings were presented in a ratio of 10:1, and participants had to decide intuitively whether the pseudoword matched the picture (Breitenstein et al., 2004; Flöel, Rösser, Michka, Knecht, & Breitenstein, 2008). Following one hour of training, participants completed a test of lexical knowledge, in which they heard the name of each object in their native language followed by the pseudoword, and decided whether the pairing represented a correct or incorrect translation, and a free recall test in which they named objects using the newly learned pseudowords. Breitenstein et al. (2004) reported that participants achieved a mean score of 83% on the test of lexical knowledge and on average were able to name 38% of pictures using pseudowords in the free recall test. However, importantly, in these studies the implicit language training took place within the context of a functional MRI scan (Breitenstein et al., 2004), or during non-invasive cortical stimulation protocols (Flöel et al., 2008). Accordingly, although these highly controllable studies of pseudoword learning imply that lexical knowledge may be achieved through brief sessions of auditory-visual word-object pairings, such studies may lack ecological validity as pseudowords may lack the phonologic complexity and diversity of words in natural languages, limiting conclusions that can be drawn regarding actual lexical learning. Thus, there remains little evidence to guide appropriate training and expectations at the earliest stages of L2 learning.

2.2.3 COMPONENTS OF SUCCESSFUL LANGUAGE TRAINING PROGRAMS

At a very basic level, L2 learners are faced with a number of challenges such as adding newly acquired vocabulary to an existing verbal lexicon, and adults learning an L2 for the first time often have an especial difficulty with perception and production of foreign speech sounds (Rast, 2008). Several researchers have argued that specific instruction in proper pronunciation of novel speech sounds may be necessary for adult L2 learners to master the phonological component of learning foreign vocabulary (Nicolaidis & Mattheoudakis, 2012; Pennington, 1998; Silveira, 2002). For example, in a study in which Francophone adults were trained to distinguish the voiced /ð/ and voiceless /θ/ sounds of English, three sessions of recognition training combined with feedback resulted in significant pre- to post-training improvements in identification and discrimination (Jamieson & Morosan, 1986). Nicolaidis and Mattheoudakis (2012) also recommend teaching pronunciation concurrently with vocabulary by categorizing new words according to a phonological aspect of the word. For example, at the beginner level they suggest categorizing concrete nouns according to vowel sounds.

Previous research has demonstrated that repetition of speech plays a fundamental role in learning by mapping auditory and sensory input onto matching motor output (Hickok & Poeppel, 2004), and Peters (2012) has underscored the importance of multiple encounters with new words to allow for more opportunities for retrieval and consolidation of meaning. Repeated practice of novel material has been shown to be important in reinforcing lexical knowledge gained during L2 learning (DeKeyser, 2007) improving verbal fluency in an L2 (VanPatten & Cadierno, 1993), and is predictive of overall language competence in an L2 (Bialystok, 1981).

Output practice, specifically, which involves actually verbalizing words in the L2 has been hypothesized to be particularly important to L2 acquisition as it may push learners to process language more deeply (Kitajima, 2001; Swain, 1985, 1995, 2000). For example, five university students were trained to learn 39 target L2 verbs over the course of two weeks, 20 in an output condition and 19 in an input condition. All verbs were taught through the use of a silent video. Words in the input condition were presented by the instructor, who explained the usage of each word and then asked questions that contained a target word; students were not required to use the target words when responding to questions. Words in the output condition were presented and explained by the instructor as in the input condition;

students then engaged in small group discussion in which they were required to use each target word once in context, and were also asked to talk about the video and use the target words individually in front of the class. Results indicated that two and one half months after training, more of the words learned through direct instruction combined with output practice were recalled, and subsequently used when students were asked to spontaneously generate question than words taught in the input condition (Kitajima, 2001).

It is also important to differentiate between meaningful and mechanical practice. In contrast to mechanical drills, which need not necessarily be understood by learners to provide the correct response, meaningful practice requires that the learner understand what is being said in order to complete the drill (Paulston & Bruder, 1976), leading to a deeper understanding of content (DeKeyser, 2007). In fact, it has been suggested that the most effective training programs are those that require learners to actually *use* newly learned words in a "real world" context that is meaningful (e.g. during conversation or in the context of a sentence), rather than those that simply expose learners to target words (Chomsky, 1965; DeKeyser, 2007; Hulstijn & Laufer, 2001; Laufer & Rozovski-Roitblat, 2011; Laufer-Dvorkin, 2006; Peters, 2012).

In addition to meaningful practice, literature on the use of feedback in L2 instruction indicates that corrective feedback has a significant positive effect on L2 acquisition in general (Leeman, 2003; Li, 2010; Nicholas, Lightbown, & Spada, 2001; Russell & Spada, 2006). In a meta analysis of 22 published studies and 11 PhD dissertations, Li (2010) investigated the use of corrective feedback on subsequent L2 performance. He reported a medium overall effect of corrective feedback on performance, which was maintained during follow up testing. It was noted that this effect was better maintained for implicit (e.g. clarification) than explicit feedback (e.g. overt indication that a response was incorrect) over time. An example of implicit corrective feedback is the use of recasts, or rephrasing an incorrect learner response in terms of the correct response (Li, 2010). Recasts in particular have been found to promote retention of learned material over time (Leeman, 2003; Li, 2010), particularly when the context in which they are presented is clear (Nicholas et al., 2001). As well, feedback provided by a teacher, a native speaker or computerized feedback did not differ in terms of efficacy (Li, 2010).

In line with findings reviewed above, it has been suggested that an effective language-training program should include explicit instruction that is both meaningful and language-focused, combined with output tasks that are meaningful and that serve to develop fluency in the target language (Nation, 2001, 2007). Thus, a program that includes instruction on correct pronunciation (Nicolaidis & Mattheoudakis, 2012; Pennington, 1998; Silveira, 2002), systematic and meaningful practice of novel lexical items (Bialystok, 1981; DeKeyser, 2007, 2010; VanPatten & Cadierno, 1993), and immediate constructive feedback on performance (Leeman, 2003; Li, 2010; Nicholas et al., 2001; Russell & Spada, 2006) is likely to be effective in promoting L2 learning, particularly in the early stages of learning (Dekeyser & Criado, 2013).

2.2.4 COMPUTER-BASED LANGUAGE-TRAINING

Beyond important considerations in L2 training protocols, an increasingly discussed topic in SLA research constitutes technological advances in delivery of L2 instruction. Given the increasing market for L2 learning, combined with rapid advances in technology, a variety of computer-based language-training software is available (See Eskenazi, 2009 and Godwin-Jones, 2009, 2011 for discussions of currently available software). However, there remains a dearth of empirical research evaluating the relative efficacy of language learning software. Limited, preliminary research has indicated that software programs may be effective in promoting L2 acquisition for some individuals. For example Vesselinov (2009) found that of 135 individuals using the *Rosetta Stone* software to learn Spanish as a second language, 64% demonstrated statistically significant gains in performance relative to pre-training on a Spanish language test after 55 hours of training, although no gains were reported for the remaining 36% of the sample. Further research that compares the efficacy of various types of computer-based training across a range of participants is required before definitive conclusions can be drawn.

Current computer-based language-training programs draw on the principles of reinforcement through repeated exposure to novel lexical items, provide instruction of phonetic components of language, and use visual information to provide a clear context for new learning, with increasing levels of complexity that build on prior learning (Saury, 1998). However, despite strong support in the literature on the importance of actually using newly acquired language to support

L2 acquisition (de Bot, 1996; Hulstijn & Laufer, 2001; Laufer & Rozovski-Roitblat, 2011; Peters, 2012; Swain, 1985, 1995), few computer-based programs incorporate speech recognition software that can provide immediate feedback to learners. Furthermore, although, as reviewed above, constructive feedback during training is an important component of L2 training (Leeman, 2003; Li, 2010; Nicholas et al., 2001; Russell & Spada, 2006) the efficacy of speech recognition in computerized L2 training has not been examined in the published literature.

Although automatic speech recognition (ASR) is commonly used to interpret the meaning of speech, there may be limitations to interpretation of speech that is heavily accented or non-fluent, as in the case of an L2 learner (Godwin-Jones, 2009). Early versions of speech recognition software applied to learning have encouraged learners to speak in such a way that a waveform or pitch contour of their speech patterns approximate that of a typical native speaker, which is presented alongside (Godwin-Jones, 2009). However, such displays may be difficult for a learner to interpret, and may be limited in their ability to detect subtle differences in pronunciation or offer specific feedback to guide improvement.

Recently, Kumar and colleagues reported on a study in which they used language learning software developed for use on a mobile phone, with speech-recognition software specifically adapted for use with children in rural India (Kumar, Reddy, Tewari, Agrawal, & Kam, 2012). The authors adapted speech recognition software to account for the specific accents typical of their sample by collecting a speech corpus of 6250 utterances from representative speakers and adapting the speech recognizer to account for variations in speaking rate and articulation, resulting in a 91.4% accuracy rate overall. In their study, children participated in one of two conditions: receptive training, in which children recognized the meaning of the word, or productive training, in which children verbalized the word. Although both conditions resulted in improved recognition of the correct meaning for the words relative to pre-training, children in the productive training condition were able to learn more words than those in the receptive training condition (Kumar et al., 2012).

Although these findings further emphasize the importance of functional speech recognition software and feedback for computer-based language training programs, in a broad audience of L2 learners, basing correct responses on those of other, heavily accented learners would likely limit the development of native-like pronunciation, which is often a goal of L2 learning. Thus, utilizing a speech-recognition paradigm in which the criteria for accurate pronunciation can be made increasingly stringent over time may serve to shape pronunciation as learners advance (Neri, Cucchiarini, Strik, & Boves, 2002).

2.2.5 AGE AND SECOND LANGUAGE ACQUISITION

It has been hypothesized that a critical or sensitive period exists for L2 acquisition, based on the apparent difficulty for those who learn an L2 in adulthood to achieve native-like facility in the L2. However, there have been many suggested definitions of critical period, and several proposed mechanisms by which L2 acquisition may be constrained. Furthermore, the results of research that has investigated a critical or sensitive period for L2 acquisition are often complex and even contradictory, and several researchers have reported counterexamples to the critical period hypothesis (See for reviews Abrahamsson & Hyltenstam, 2009; Birdsong, 2006; Singleton & Ryan, 2004). A number of studies have demonstrated a significant negative correlation between age of acquisition and L2 proficiency, with correlations ranging from -.45 to -.77 (Abrahamsson & Hyltenstam, 2009; Birdsong & Molis, 2001; DeKeyser, 2000, 2010; Hakuta, Bialystok, & Wiley, 2003; Johnson & Newport, 1989; See Birdsong, 2006 for a review); and age of acquisition has reliably been identified as the strongest predictor of ultimate L2 attainment (Birdsong, 2006). However, although there is a clear linear relationship between age and L2 acquisition across the lifespan, results are less clear in terms of an effect of age on L2 acquisition after puberty.

In the seminal work by Johnson and Newport (1989), the linear relationship between age of arrival (AoA) in the United States and performance on a grammaticality judgment task was driven primarily by a high correlation in those who arrived prior to the age of 16, but the relationship reached a plateau for those who arrived after age 16. In an attempt to replicate these earlier findings, Birdsong and Molis (2001) reported the opposite pattern, a null relationship for those who arrived prior to age 16 but a significant negative correlation (r = -.69) between AoA and grammaticality judgment for individuals who arrived between age 16 and 44. Likewise, Hakuta et al. (2003) found no discontinuity across the lifespan in the linear relationship between AoA and English proficiency.

A linear relationship between AoA and performance on an L2 grammaticality judgment test has also been demonstrated in a cross-linguistic sample of native Russian speakers learning English or Hebrew as a second language (DeKeyser, Alfi-Shabtay, & Ravid, 2010). Although Dekeyser and colleagues reported a flattening of the slope of age of acquisition and attainment between adolescence and adulthood, this finding may reflect the apparently arbitrary division of adults into ≤ 40 and > 40 categories, resulting in a restricted range of adults over the age of 40. Visual inspection of the graphically depicted data presented in their paper suggests that a linear relationship may have been present had they analyzed results from all adults aged ≥18 as a group (DeKeyser et al., 2010).

2.2.6 WORKING MEMORY, PROCESSING SPEED, AND SECOND LANGUAGE ACQUISITION

Cognitive abilities such as general attention, working memory, and processing speed may influence performance on complex tasks that involve learning new information (See Bäckman, L., & Farde, 2005 for a review). Thus, in explaining the relationship between age and early L2 acquisition, it is necessary to also consider a range of factors, such as working memory and processing speed; skills that may contribute to L2 acquisition (Cain, Oakhill, & Lemmon, 2004), and that have been found to correlate negatively with age (Bowden, Sanz, & Stafford, 2005; D. C. Park et al., 2002; Wechsler, 2008). Working memory, in particular the phonological loop, which involves both storage and rehearsal of new verbal information, is hypothesized to play a role in learning the novel phonological forms of new words (Baddeley, Gathercole, & Papagno, 1998; Baddeley, 2003). Several studies have demonstrated a link between verbal working memory and L2 vocabulary learning (Kormos & Sáfár, 2008; Papagno & Vallar, 1995; Service, 1992). For example, Papagno and Vallar (1995) reported that polyglot adults had higher performance on working memory tasks than non-polyglots; they also reported a relationship between verbal working memory as measured by digit span and nonword repetition, and the acquisition of new words in an L2. Likewise, performance on backwards digit span was correlated with performance on a test of L2 vocabulary in adolescents who were learning an L2 at the beginner level (Kormos & Sáfár, 2008), although there was no relationship between L2 learning and phonological non-word span.

However, we are not aware of any studies that have explicitly examined the relationship between scores on cognitive tests that examine processing speed and L2 acquisition. Additionally, other factors such as amount of exposure to a language, level of education, and life experiences in general, may also interact with age in predicting L2 learning (Hakuta et al., 2003; Singleton & Ryan, 2004).

2.2.7 THE PRESENT STUDY

This study is part of a larger-scale project, which uses a computer-based language-training program called LANGA (LANguage GAming) combined with a fine-grained speech analysis engine that is capable of providing specific feedback to students on pronunciation and intonation for individual words as well as continuous speech. This innovative design allows learners to practice oral expression in the target language and receive immediate feedback on their verbal performance. As reviewed above, practice and feedback are components of language learning that have been identified as necessary for effective communication in the target language (Bialystok, 1981; DeKeyser, 2007; Leeman, 2003; Li, 2010). The primary goal of the present study was to determine how accurately adults are able to learn novel vocabulary presented during intensive computer-based training in an explicit learning condition.

We hypothesized that a language-learning task in which participants are provided with acoustic-visual pairings of novel Spanish words and feedback on their pronunciation of these words via speech recognition software would result in strong lexical retrieval of novel words following training and accurate pronunciation of those words. We also hypothesized, based on studies that have demonstrated a significant negative correlation between age of acquisition and L2 proficiency (Birdsong & Molis, 2001; DeKeyser et al., 2010; Hakuta et al., 2003) that younger participants would demonstrate a higher capacity for learning than older participants. Additionally, although we are aware of no studies that have reported a specific relationship between L2 vocabulary learning and any measures of working memory and processing speed, we hypothesize that faster times on measures of processing speed and higher scores on working memory tasks will predict lexical learning.

2.3 METHODS

2.3.1 PARTICIPANTS

Thirty-four healthy right-handed participants (12 women, mean age 43.7, SD 10.6) who ranged in age from 26 to 65 years provided informed consent and were included in this study. All participants were unilingual native English speakers with no previous training in Spanish, and were recruited locally through multi-media advertisements or through word of mouth. Participants had on average 17 years of formal education (SD = 2.7), and performed in the average to superior range on the majority of working memory and processing speed tests including Trail Making Test A and B (Reitan & Wolfson, 1985, 1993), Digit Symbol Coding and Letter Number Sequencing from the WAIS-III (Wechsler, 1997a), and Spatial Span from the WMS-III (Wechsler, 1997b). Descriptive statistics for participants are presented in Table 2.1.

2.3.2 PROCEDURES

2.3.2.1 Training Content

A pool of 48 Spanish nouns and verbs were selected for inclusion in the present study based on criteria that included: the ease with which the words could be visually depicted; lack of similarity in sound to their English counterparts (i.e. non-cognates); not likely to be encountered outside formal Spanish training (e.g., *uno*, *dos*, *tres*); containing no more than one phoneme that would be new to an English speaker with no prior exposure to a romance language. Additionally, only verbs that were regular in both the third person singular and third person plural were included (although only the third person plural form was ever presented to participants in this study). A list of words included in the LANGA training protocol is included in Appendix A. Words were distributed across two training sessions such that each training session contained a total of 16 nouns and eight verbs. Nouns were presented as coloured line-drawings whereas verbs were presented as colourless line-drawings in order to emphasize the action rather than the generic, featureless individual performing the action. Images were all original artwork produced by Copernicus Studios, Inc. (Halifax, NS), who developed the LANGA software.

To ensure a lack of prior exposure to Spanish, each participant completed a baseline test in which they were asked to name the pictures included in the training set. No participant was able to produce any of the Spanish words to be learned.

2.3.2.2 LANGA Training Protocol

Training was delivered through LANGA, a set of video games and animated tutorials co-developed by our lab and Copernicus Studios, Inc. using the Flash software platform (www.adobe.com/products/flash). Naming accuracy was assessed by commercial speech recognition software (Telisma; Paris, France). The speech recognition engine (SRE) uses machine learning algorithms to guess which word was spoken (chosen from a list of possible candidate words provided to the SRE from the game), and produce a confidence score (on a scale of 1–100) for that guess. The SRE was trained on a large sample of native and non-native Spanish speakers, with the intention of being robust to a variety of accents including non-native speakers. For the LANGA training games, words were trained in groups of four and the list of possible candidates provided to the SRE on any given trial was limited to the four items being trained in that set. The SRE confidence threshold was initially set to 40 for each word; this was chosen based on pilot testing to ensure that the SRE would differentiate between correct and incorrect words, yet allow for minor distortions in pronunciation or heavily accented responses. Preliminary data from a pilot study in our lab using a previous version of LANGA suggested that most subjects could accurately name a high percentage of pictures of the words they were trained on, even after only 2 days of training (though in those studies only 12, rather than 24, words per day were trained).

Participants were taught word-picture associations through an auditory demonstration of the correct pronunciation of novel words paired with their target pictures. Participants were permitted to hear the demonstrations at their discretion as many times as needed until they were confident that they could remember the Spanish word-object pairings. Learning was followed by a series of mini-games in which participants were drilled on the word-object pairings through games, which require the naming of pictures. These games involved matching to a target, identifying duplicate pictures, and recalling missing items. Each training session was concluded with a review of words learned to that point. Visual feedback was provided to participants following each vocal response they made, in the form of an image of an intact heart for correct responses, or a broken heart for incorrect responses. After a second incorrect response for any particular item, a “recast” was provided in which the participant was able to hear the pronunciation of the target word and see the correct spelling of the word paired with the target picture.

Training took place over two consecutive days and consisted of sessions that lasted approximately 60 minutes each. Participants were seated in front of a laptop computer in a private office and wore a Logitech (Morges, Switzerland) headset with a microphone to record verbal responses. Prior to the first session, participants viewed an animated tutorial that explained the basics of the LANGA training program. Additional animated tutorials were presented throughout the training sessions that explained the basics of individual games.

2.3.2.3 Outcome Measures

Following the second training session, Spanish naming ability was assessed using a naming task in which all 48 pictures were presented one by one, in random order for 4 seconds each with an interstimulus interval of 1 second using Presentation software (Version 16.3 Build 12.20.12; http://www.neurobs.com). Each participant was asked to name the images in Spanish, and to try his or her best to name each picture. Responses were recorded on the computer using the Logitech headset, and later scored on a 5-point likert scale according to the following criteria: A perfectly pronounced and accurately recalled word and it’s preposition received 4 points; a perfect word with an absent or incorrect preposition, or a word that was almost perfect save for a slight deviation in pronunciation received 3 points; if the word uttered was clearly imperfect, but still recognizable as the target word, two points were awarded; a word that was clearly not correct, but that did resemble the target word in some way received 1 point; and words that did not resemble the target word in any way, or no response received a score of 0. Scoring of each sound file was conducted by a minimum of two raters working independently, none of whom knew Spanish prior to working on this project. Initial inter-rater reliability was measured at κ = .75; however the scores from one of the six raters involved in project were discrepant from those of other scorers (i.e. the rater appeared to have scored the wrong files). Thus, in the event of a word scoring discrepancy greater than one point, the word was scored by a third party who was familiar with the training words to reduce the discrepancy, improving inter-rater reliability to κ = .81.

2.4 RESULTS

As described above, each of the 48 Spanish words was scored on a 5-point likert scale that ranged from 0 to 4. Across participants, post-training scores ranged from a total naming score of between 20 and 139 of a possible 192 points (mean = 83.35, *SD* = 28.75). Overall, the participants in this study were able to name between 4 and 36 words, and averaged approximately 18.32 words (*SD*=7.37), or 38.2 % of the target words, as evidenced by the number of words that were awarded a score of either 3 or 4 points in the post-naming Spanish test. As with overall naming score, the number of words recalled during the naming test was significantly correlated with both age (r = -.491, p = .003) and with Digit Symbol Coding (r = .620, p < .001). Using more relaxed criteria that indicated that participants had some knowledge of the target word despite inaccurate pronunciation (words scored between 2 and 4 points), participants named between 6 and 43 of the 48 words correctly, and averaged 26.53 words (*SD* = 8.41), or 55.2% of the target words.

2.4.1 PREDICTORS OF LEXICAL LEARNING

To determine whether there was a relationship between number of syllables in the Spanish words and lexical retrieval, we conducted a correlation analysis between the number of syllables in each word and the score that each participant achieved on each word. There was a significant negative correlation ($r = -.280$, $p < .001$) between word score and number of syllables, indicating that words with fewer syllables were recalled more frequently with more accurate pronunciation than words with more syllables. The frequency of word score and number of syllables for each of the Spanish vocabulary items are presented in Appendix A.

Given the relatively small sample size in this study (n = 34; Allison, Primavera, & Louis, 1993), we conducted a backward regression analysis to determine whether any relationship existed between demographic variables, performance on neuropsychological testing and Spanish vocabulary learning.[1] In this approach, the least significant predictor variables are removed one-by-one until only significant predictors remain. The order of removed variables was as follows: Spatial Span (B = .140, $p = .931$), Trail Making Test-B (B = .236, $p = .603$), Letter Number Sequencing (B = .807, $p = .676$), and Trail Making Test-A (B = -.685, $p = .336$). The remaining variables (Age, Digit Symbol Coding, and years of education) predicted lexical retrieval of Spanish words following two sessions of LANGA, F (3,

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[1] Because multiple regression is known to be influenced by issues related to departures from normality, heteroscedasticity, and multicollinearity, all predictor variables were examined to ensure that the assumptions of normality and homogeneity of variances were met using partial regression plots, measures of skew and kurtosis, and VIF values (Tabachnik & Fidell, 2007). There were no problems with multicollinearity; all VIF values were below 5 for all predictors, and correlations among predictors were low to moderate.

30) = 9.80, $p < .001$, $R^2 = .495$. Age was a significant negative predictor of Spanish lexical retrieval (B = -1.078, $p = .012$; Figure 2.1) whereas the raw number of items completed on the Digit Symbol Coding subtest within a two-minute time limit positively predicted lexical retrieval (B = 1.060, $p = .003$; Figure 2.2). Although Years of Education was retained in the model, it did not emerge as a significant predictor of lexical retrieval (B = -2.681, $p = .089$). A correlation matrix of Spanish naming score and all predictor variables is included in Table 2.2, and results of the backwards regression are presented in Table 2.3.

2.5 DISCUSSION

This study was designed to measure the effects of a computer-based language-training program on L2 vocabulary learning. The findings obtained through this study indicate that participants were able to learn a number of novel words through word-picture associations, and subsequent vocalization of the novel words, but that significant variability existed within our sample of participants in terms of vocabulary acquisition.

We hypothesized that adults who participated in the LANGA training program would demonstrate high lexical retrieval and accurate pronunciation of trained Spanish vocabulary. Our results indicated that participants learned on average, approximately 18 or 26.5 words over the two LANGA sessions depending on the criteria used. Previous research has found that on average, university students were able to learn and subsequently recognize approximately 36 novel pseudowords that were paired with objects in a single implicit training session, and explicitly recall approximately 17 of those pseudowords (Breitenstein et al., 2004; Flöel et al., 2008). However, there has been no comparison of the ecological validity of learning pseudowords in an experimental context as opposed to words from a foreign language, and no previous research has examined the capacity for early learning of L2 vocabulary or pseudowords in adults using an explicit training paradigm. Thus it is difficult to draw a direct comparison across studies.

The 38% success rate for lexical retrieval with strict criteria for accurate pronunciation, and the 55% success rate for lexical retrieval without strict criteria for pronunciation in the present study likely reflects the difficulty of learning a large number of complex novel words and phonemes over a brief period of time. In the present study, our participants had no prior training in Spanish and were asked to learn 24 words in each session, for a total of 48 words. Thus, low overall naming scores may reflect an effect of overload in which the amount of information to be learned overwhelms the learner and inhibits efficient learning, particularly during the initial stages of language acquisition. However, previous research in which only 12 novel words were taught to higher proficiency L2 learners in high school over a 90 minute session using an explicit, vocabulary-based protocol indicated that students were able to provide the correct L2 word in response to a corresponding definition for between 60 and 68% of the words (Laufer-Dvorkin, 2006). Thus, it is also possible that the capacity for novel lexical learning is limited regardless of proficiency level. The present study provides a real-world estimate of initial capacity for vocabulary learning in monolingual adults across a wide range of ages (Figure 2.1).

2.5.1 WORD STRUCTURE AND LEXICAL LEARNING

An aspect of second language acquisition that appears to be overlooked in the literature is the influence of the number of syllables in target words on vocabulary acquisition. Whereas studies of pseudoword learning have reported using pseudowords that consisted of four letters and two syllables each (Breitenstein et al., 2004; Flöel et al., 2008), we are aware of no studies investigating vocabulary acquisition in natural languages that have reported any effect of syllable count on target word acquisition. In the present study, there was a significant negative relationship (r = -.280) between the number of syllables present in target words and successful naming of associated pictures. For example, whereas 27 participants were awarded a score of 0 and no participants were awarded a score of 4 for the word *El Basurero* (5 syllables), 15 participants were awarded a score of 4 and only 4 participants received a score of 0 for the word *Ama* (2 syllables). Notably, the only word that was recalled to some degree by all participants was the word *El Pez*, and no participant received a perfect score for the words *El Leñador* or *El Sacerdote*. Thus, words with more complex syllable structure may require additional practice than simpler words, and the number of syllables per word should be taken into consideration in the earliest stages of L2 training.

However, it is possible that some naming difficulties may have stemmed from challenges that some participants had in recognizing some of the pictures to be named. Specifically, participants had difficulty naming both *Judge* (el Juez) and *Priest* (el sacerdote), both of which were depicted as featureless characters wearing a black robe, one with a gavel and one with a priest's collar. During training, several participants mentioned having difficulty distinguishing between these two characters; thus the lack of distinctive characteristics between the two may have made recall more difficult during picture naming tasks in which pictures were presented in random order. Therefore, we recommend that future studies use rigorous pilot testing to ensure that all pictures are unequivocally representative of the word that is being taught.

In addition to some specific perceptual difficulties, it was noted that participants had a particular difficulty pronouncing Spanish words containing phonemes that differ markedly from English phonemes. For example, words containing /ɲ/ and /ʎ/ were among some of the words that proved most difficult to learn, in that many people received a score of 0 and few people received a score of 3 or 4. This finding supports recommendations that proper pronunciation be taught during L2 instruction (Nicolaidis & Mattheoudakis, 2012; Pennington, 1998; Silveira, 2002), as specific instruction on aspects of L2 pronunciation may serve to facilitate vocabulary acquisition and enhance pronunciation (Erlam, 2003).

2.5.2 PREDICTORS OF LEXICAL LEARNING

Our hypothesis that vocabulary learning would be related to processing speed and working memory was only partially supported. Results of a multiple regression analysis to evaluate the relative contribution of age, education, working memory and processing speed to vocabulary learning revealed that age negatively predicted lexical retrieval and raw score on the Digit Symbol Coding test of the WAIS-III (Wechsler, 1997a) was a positive predictor of lexical retrieval. Across our sample of participants the strongest predictor of Spanish naming performance was raw score on the Digit Symbol Coding test of the WAIS-III (Wechsler, 1997a), which measures speed of information processing, and includes components of motor speed, visual search, and incidental learning (Lezak, Howieson, Bigler, & Tranel, 2012).

Consistent with previous research (Bialystok & Miller, 1999; DeKeyser et al., 2010; Hakuta et al., 2003), our results also reflect a reduced capacity for language acquisition with age, as age was a negative predictor of lexical retrieval in our sample. The correlation coefficient for age and naming score in the present study (-.56) is only slightly smaller than that reported by Birdsong & Molis (-.69; 2001), who investigated the relationship between AoA and L2 acquisition in late learners over the age of 16.

Despite modest evidence of native-like attainment among late learners in some aspects of the L2 (Birdsong & Molis, 2001) the majority of research shows a negative relationship between L2 attainment and age of acquisition across the lifespan (Abrahamsson & Hyltenstam, 2009; Birdsong & Molis, 2001; DeKeyser et al., 2010; Johnson & Newport, 1989). The literature on age effects in L2 acquisition often uses neurological arguments, such as a loss of neural plasticity, to explain the apparently less successful L2 acquisition in adults than in children (See Birdsong, 2006 and Singleton & Ryan, 2004 for reviews). However, few studies have made the distinction between learning a foreign language and learning a second language in the context of immersion. For example, previous studies that have investigated AoA in the United States have not always considered the amount of exposure that immigrants have to the language of their host country, or potential differences in motivation to learn the language. These variables will be important to define operationally and investigate in future research that examines the effect of age on L2 learning.

2.5.3 LIMITATIONS AND FUTURE DIRECTIONS

As with previous research, our study was limited to a relatively small sample of highly educated participants, which may not reflect the population at large (DeKeyser et al., 2010). However, it is important to note that unlike previous studies investigating factors associated with L2 proficiency, we were able to control for length and amount of exposure to Spanish, as well as age of acquisition vs. age of testing, as our participants were all naive to Spanish vocabulary prior to training, and all experienced only two sessions of LANGA, which lasted approximately one hour each.

It is generally understood that acquisition of syntax and higher level language processing relies on a foundation of lexical knowledge that consists of speech perception and object-meaning association (Siskind, 1996), therefore, a general understanding of individual capacity for acquisition of basic lexical knowledge is an important foundation to developing effective methods for L2 instruction. Although we were able to control for the amount of L2 training input that each participant received we were unable to control for the amount of L2 intake, or how much each participant was able to learn; thus, despite a consistent level of exposure to the Spanish words, our participants demonstrated a wide range of proficiency across performance on Spanish naming tests. Future research that investigates factors beyond processing speed and working memory that may be associated with L2 intake, such as language fluency in L1 may lead to development of training programs that can be better customized to individual needs.

The training protocol used in the present study was limited to explicit, training of single word-picture associations over two intensive training sessions. It would be beneficial for future studies to also investigate the efficacy of implicit and grammatical training protocols. Indeed research that is currently underway in our lab will help to shed light on the benefits of implicit vs. explicit computer-based language instruction with a grammatical component across a range of ages, while controlling for previous L2 exposure. It is hoped that our research will eventually include cross-linguistic exposure (i.e. participants with different L1 backgrounds who are learning a common L2), or multiple L2s to compare results across languages. Further research investigating more comprehensive language-training protocols, as well as "real world" application of language learning may assist with the development of effective programs for foreign language acquisition.

2.5.4 CONCLUSION

This study aimed to explore the effectiveness of a computer-based language-training program on Spanish vocabulary acquisition. Learners were presented with paired word-picture associations and then required to use the target words in a series of computer-based games; feedback was provided following each word.

Findings indicate that participants were able to learn and subsequently retrieve novel words acquired using this method of instruction, however retention of Spanish words following instruction was negatively related to age, and speed of information processing. Although future research with more sophisticated training protocols is necessary in the development of effective computer-based training programs, the present study provides evidence of initial capacity for foreign word learning in the context of computer-based learning using speech recognition-based feedback to learners.

Table 2.1.

Descriptive statistics for demographic variables.

	Mean	SD	Range
Age at time of study	43.65	10.63	25 – 65
Education (years)	17.00	2.72	12 – 25
Handedness	84.63	15.43	50 – 100
Trail Making Test-A (z-scores)	0.54	0.72	-1.43 – 1.60
Trail Making Test-B (z-scores)	0.67	0.96	-1.48 – 2.34
Digit Symbol Coding (WAIS-III)	12.5	2.36	8 – 16
Letter Number Sequencing (WAIS-III)	11.44	2.38	8 – 18
Spatial Span (WMS-III)	13.03	2.26	8 – 17

Note. Handedness score obtained using the Edinburgh Handedness Inventory (Oldfield, 1971). Tombaugh (Tombaugh, 2004) norms were used to calculate z-scores for the Trail Making Tests. Scaled scores for Digit Symbol Coding and Letter Number Sequencing were obtained from the WAIS-III Administration and Scoring Manual (Wechsler, 1997a), and scaled scores for the Spatial Span subtest were obtained from the WMS-III Administration and Scoring Manual (Wechsler, 1997b). All participants performed in the average range or above on all tests, with the exception of three participants who had one below average score each: one on Trail Making Test A and two on Trail Making Test B.

Table 2.2.

Correlations among Spanish naming scores and predictor variables.

	Naming	Age	Educ	EHQ	TMT-A	TMT-B	DS-C	LN
Age	-.558**							
Education	.076	-.302						
EHQ	.075	.124	-.137					
TMT-A	-.364*	.160	-.255	.158				
TMT-B	-.363*	.248	-.211	.176	.396*			
DS-C	.583**	-.472**	.419*	-.040	-.512**	-.694**		
LN	.295	-.252	.052	.067	-.107	-.428*	.324	
SSpan	.204	-.235	.009	-.284	-.016	-.120	.210	.218

Note. Years of education (Educ), Handedness score from the Edinburgh Handedness Questionnaire (EHQ), Trail Making Test A and B (TMT-A; TMT-B), Digit Symbol Coding (DS-C), Letter-Number Sequencing (LN), Spatial Span (SSpan).

* $p \leq .05$

** $p \leq .01$

Table 2.3

Predictors of lexical retrieval of novel Spanish vocabulary

	Predictor	B	SE beta	*p*	Partial *r*	VIF	R Square Δ	F
	Age	-1.078 *	.402	.012	-.440	1.31		
	DSC	1.060**	.330	.003	.506	1.44		
	Educ	-2.681	1.524	.089	-.306	1.23		
							.495	9.80**
Removed	SSpan	.140	1.596	.931	.017	1.13		
	TMT_B	.236	.450	.603	.101	2.21		
	LN	.807	1.913	.676	.079	1.15		
	TMT_A	-.685	.700	.336	-.179	1.38		

Note. DSC, Digit Symbol Coding from the WAIS-III; Educ, years of education; SSpan, Spatial Span from the WMS-III; TMT_B, Trail Making Test B; LN, Letter-Number Sequencing from the WMS-III; TMT_A, Trail Making Test A and B. For all predictors, raw scores were used.

* $p \leq .05$

** $p \leq .01$

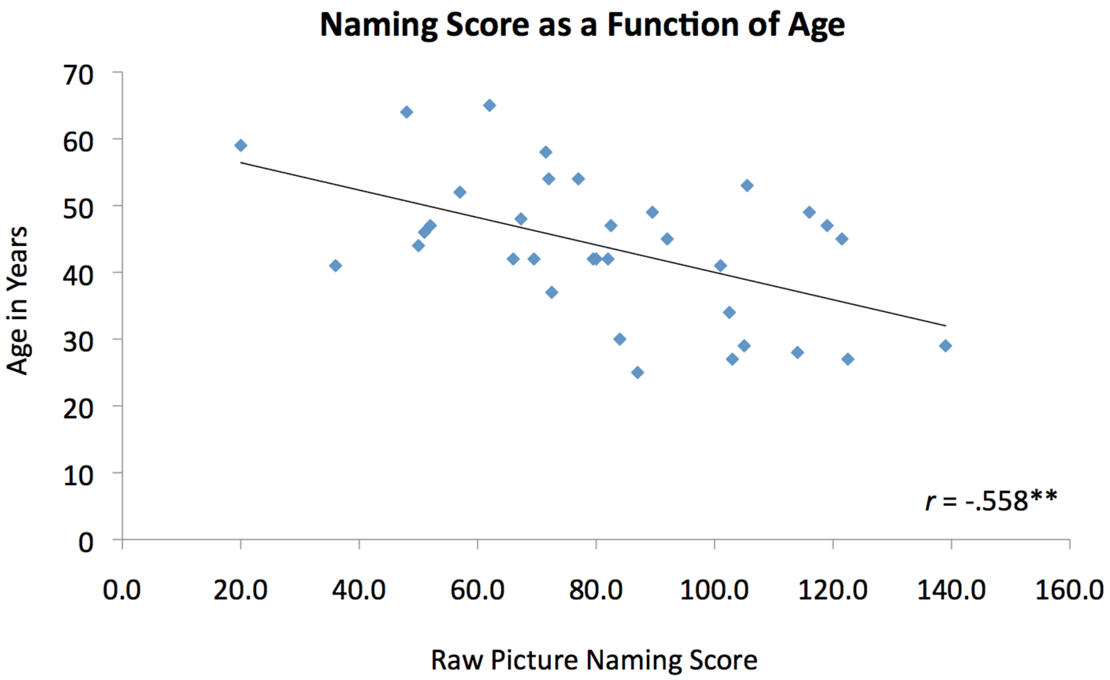

Figure 2.1. Post training Spanish picture naming scores as a function of age.

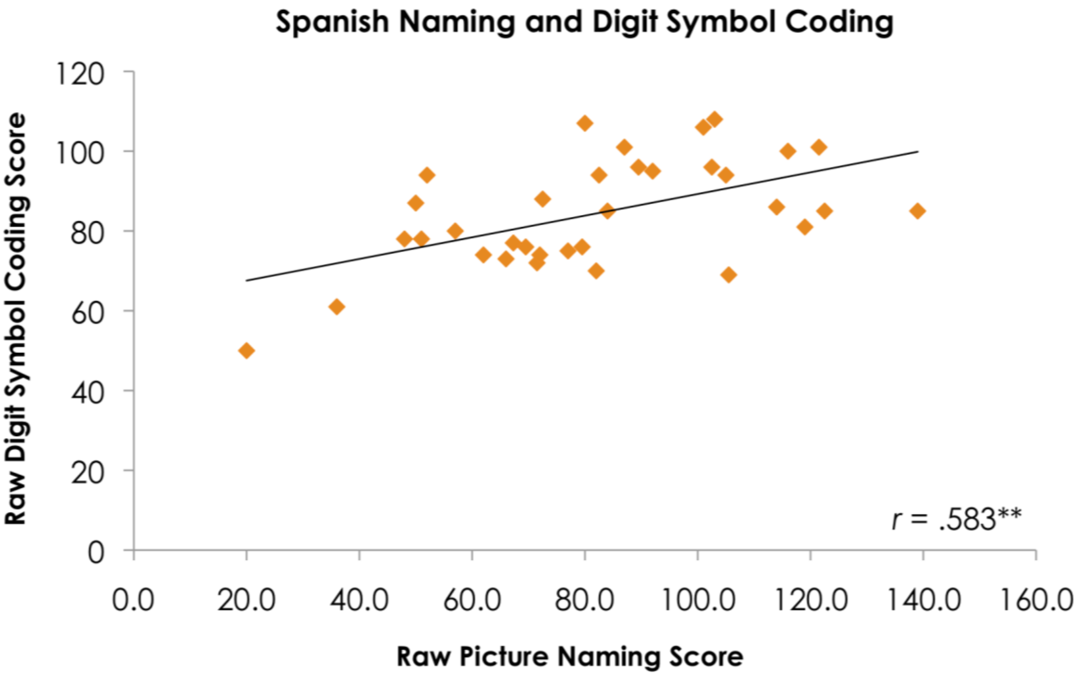

Figure 2.2. Post training Spanish picture naming scores as a function of performance on a test of Digit Symbol Coding.

2.6 SUMMARY AND LINKING STATEMENT FOR CHAPTER 3

Chapter 2 revealed that the participants in this thesis project were able to learn a number of Spanish words using a computer-based language-training program called LANGA. There was a large range in overall vocabulary acquisition across participants, and learning was influenced by both age and speed of information processing, as measured by the Digit Symbol Coding subtest of the WAIS-III (Wechsler, 1997a). Based on the low number of perfect word scores awarded during a Spanish naming test across the sample of participants, results are consistent with our hypothesis that Spanish naming involves effortful lexical retrieval and articulation in this sample.

In Chapter 3, this effortful Spanish language production will be further examined using an fMRI paradigm designed to elicit cortical activity present during picture naming in English and Spanish respectively, relative to a control condition. Previous research has found high levels of right hemisphere brain activity in individuals who are learning a second language, and it has been suggested that this activity is similar to that of individuals with aphasia following a left hemisphere stroke (Raboyeau et al., 2008). This chapter will investigate whether similar findings are evident in our sample of participants.

CHAPTER 3 CORTICAL ACTIVITY ASSOCIATED WITH PICTURE NAMING IN THE EARLIEST STAGES OF SECOND LANGUAGE ACQUISITION

3.1 ABSTRACT

Second language (L2) processing has been found to activate a more extensive cortical network than first language (L1) processing in low proficiency bilinguals. This study used fMRI to investigate cortical activity in 34 unilingual native English speakers who were asked to learn Spanish vocabulary for the first time. Both English and Spanish picture naming activated Broca's area in the left hemisphere (LH), and English picture naming also activated Broca's homologue in the right hemisphere (RH). Within-subject analysis of picture naming in English and Spanish revealed statistically significant spatial separation within primary language regions for peak activation during English vs. Spanish naming. At the group level, our participants showed less Spanish than English naming activity in primary language regions, but increased cerebellar activation. We argue for the activation of a cerebellar network that supports verbal working memory and/or complex articulatory processing in the early stages of L2 acquisition that precedes the enrichment plasticity associated with non-fluent bilinguals in L2 processing.

3.2 INTRODUCTION

Humans have a remarkable capacity for acquiring and using complex systems of communication. Through several decades of research involving neurological patients with language disruptions, pre-surgical language mapping, and more recent developments in non-invasive functional brain imaging technologies we have begun to understand the complex network of cortical and subcortical regions involved in the process of using language to communicate (Mesulam, 2000; Vigneau et al., 2006). Hickok and Poeppel (2000, 2004, 2007) have proposed the existence of a ventral and a dorsal pathway in the left hemisphere (LH) that are involved in speech processing. These authors suggested that the ventral pathway, which includes the temporal-parietal-occipital junction, plays a role in auditory comprehension of receptive language and provides an interface for speech input and conceptual representation. The dorsal pathway consists of inferior parietal and frontal systems, and provides an auditory-motor interface, which governs sub-lexical processes and the mapping of auditory speech onto motor representations (Hickok & Poeppel, 2000, 2004, 2007). These hypothesized pathways are consistent with literature that suggests that the three primary components of language – phonological, semantic, and syntactical – are processed in frontal, temporal, and parietal regions of the left hemisphere (See Bookheimer, 2002; Vigneau et al., 2006 for reviews).

In a meta-analysis of peak activations reported in the literature for phonological, semantic, and sentence processing, Vigneau et al. (2006), reported clusters specific to phonological processing in the dorsal portion of the pars triangularis, the supramarginal gyrus, frontal lobe regions that control mouth, pharynx, and tongue movement, and the posterior superior temporal gyrus (STG). Regions that appear to be specialized for semantic processing include the ventral pars triangularis, the pars opercularis and pars orbitalis, which have been implicated in controlled semantic retrieval (A. D. Wagner et al., 2001), the anterior fusiform gyrus, which is involved in semantic processing of words and pictures (Vandenberghe et al., 1996), and the temporal pole (Vigneau et al., 2006).

3.2.1 RIGHT HEMISPHERE INVOLVEMENT IN LANGUAGE PROCESSING

Although right hemisphere (RH) regions do not appear to have a specific function with regards phonological, semantic, or sentence processing, RH activity in the right pars opercularis and insula has been reported to co-occur during language tasks (Vigneau et al., 2011). Based on a second meta analysis in which peak activations specific to RH involvement in phonological, semantic, and sentence processing, Vigneau et al. (2011) suggested specific roles for these two areas in terms of manipulating complex material in working memory. Specifically, the right pars opercularis appears to be involved in the manipulation of complex phonological and verbal material, whereas the insula appears to support auditory attention as well as the manipulation of complex verbal, spatial, and numerical information (Vigneau et al., 2011).

Additionally, the role of the RH has been well established in both the decoding and encoding of prosody during speech (Beaucousin et al., 2007; Blonder et al., 1991; Buchanan et al., 2000; Ross & Mesulam, 1979; Ross & Monnot, 2008) and in contextual processing of language (Marinkovic et al., 2011; See Bookheimer, 2002; Lindell, 2006 for reviews). Individuals with RH lesions have demonstrated impairments in the expression of prosody (Ross & Mesulam, 1979), the ability to discriminate expressions of emotion in others (Blonder et al., 1991), or the understanding and appreciation of humour (Shammi & Stuss, 1999), highlighting the importance of the RH to non-verbal communication.

3.2.2 CORTICAL ACTIVITY ASSOCIATED WITH SECOND LANGUAGE LEARNING

A large number of studies investigating first (L1) and second (L2) language production in high proficiency bilinguals have supported that first and subsequent languages are processed by a common neural circuitry (Chee, Tan, & Thiel, 1999; Chee, Caplan, et al., 1999; Klein, Zatorre, et al., 2006; Klein, Milner, Zatorre, Meyer, & Evans, 1995; Klein, Milner, Zatorre, Zhao, & Nikelski, 1999; Klein, Zatorre, Milner, Meyer, & Evans, 1994; Liu, Hu, Guo, & Peng, 2010; Rüschemeyer, Zysset, & Friederici, 2006; See Abutalebi & Chang-Smith, 2013 and Indefrey, 2006 for reviews). In particular, both Klein and colleagues and Chee and colleagues have demonstrated evidence of a shared neural substrate for both expressive and receptive L1 and L2 processing in high proficiency bilinguals (Chee, Tan, et al., 1999; Chee, Caplan, et al., 1999; Klein, Zatorre, et al., 2006; Klein et al., 1999). For example, a comparison of brain activity during verb generation and word repetition tasks in high proficiency Mandarin (L1) – English (L2) bilinguals who learned their L2 between the ages of 10 and 14 revealed similar activation in left frontal regions for both languages, with no spatial separation of peak activity (Klein et al., 1999). These results are consistent with those of Chee et al. (Chee, Tan, et al., 1999) who reported a similar pattern of activation during Mandarin (L1) and English (L2) word stem completion tasks in high proficiency bilinguals, regardless of age of acquisition. Likewise, Liu et al. (Liu et al., 2010) reported common neural activation for both languages during a picture naming task in high proficiency Chinese (L1) – English (L2) bilinguals who began learning English after the age of 12.

In terms of receptive language, high proficiency English (L1) – French (L2) bilinguals, who learned their L2 between age 4 and 12, listened to a single word repeated five times, followed by a sixth word that represented either a change in meaning, a change in language, a change in both meaning and language, or no change. Klein, Zatorre, et al. (2006) hypothesized that if neurons were truly insensitive to language, there would be no changes in functional activity in the condition in which language, but not meaning changed. Consistent with their hypotheses they found that a change in meaning resulted in larger increases in left inferior frontal and bilateral temporal activity than a change in language. They also found some differences in adaptation, as evidenced by increased activity during forward translation (from L1 to L2) compared to backward translation (L2 to L1) in the left inferior frontal gyrus (IFG). Their findings were interpreted as reflecting a shared neural substrate for L1 and L2 at the lexical level, but with some populations of neurons within that substrate that show language a specific response (Klein, Zatorre, et al., 2006). Likewise, Chee and colleagues (Chee, Caplan, et al., 1999) reported spatially congruent fMRI activation in high proficiency Mandarin (L1) – English (L2) early bilinguals during comprehension of visually presented sentences.

3.2.3 DISTINCT CORTICAL REPRESENTATIONS FOR L1 AND L2 PROCESSING

In contrast to findings that both receptive and expressive L1 and L2 processing activate common cortical regions in high proficiency bilinguals regardless of age of acquisition, other studies have reported different patterns of cortical activity in L1 and L2 processing in bilinguals who acquired their L2 after childhood (K. H. Kim et al., 1997; Perani et al., 2003) or in non-proficient bilinguals (Golestani et al., 2006; Raboyeau et al., 2004, 2008, 2010). Kim et al. (1997) reported finding spatial separation of peak regions of activity in Broca's area in late bilinguals who learned their L2 in early adulthood, compared with overlapping activity in early bilinguals. In this study participants were instructed to describe events that had occurred at particular times during that day silently in either their L1 or L2 while undergoing fMRI. The authors suggested that age of L2 acquisition may play a significant role in determining the functional organization of Broca's area (K. H. Kim et al., 1997). However, although late bilinguals in their study were deemed high proficiency, no formal assessment of language proficiency was conducted. Golestani et al. (2006) likewise reported spatial separation of peak activity in the left IFG during covert sentence production, with greater separation for less compared to more proficient bilinguals. However, in neither case was verbal output or sentence structure across the two languages controlled.

Perani et al., (2003) reported more extensive activity for L2 than L1 production during a covert phonemic fluency task, in which high-proficiency, early bilinguals in Spanish and Catalan were asked to generate words beginning with different letters of the alphabet. Although all participants were equally proficient in both languages, the pattern of cortical activity varied as a function of whether Spanish or Catalan was the dominant language. In participants for whom Catalan was the dominant language, a comparison of L2 vs. L1 revealed more extensive activity in left frontal and parietal regions including the IFG (BA44/47), and the right IFG (BA47). In participants for whom Spanish was the dominant language, a comparison of L2 vs. L1 revealed more extensive activity in the left IFG (BA45), middle frontal gyrus, and insula. Interestingly, participants for whom Catalan was the dominant language had less exposure to their L2 than those for whom Spanish was the dominant language, which suggests that level of exposure to L2 may play a role in organization of cortical activity regardless of proficiency. An alternate explanation provided by the authors is that even when high proficiency is attained, communicating in the language acquired first in life may be less effortful than in subsequently acquired languages, which engage a more extensive network of neural resources (Perani et al., 2003).

The findings reviewed above (Golestani et al., 2006; K. H. Kim et al., 1997; Perani et al., 2003) are consistent with reports that different languages have been selectively disrupted in multilingual speakers using electrical stimulation during invasive pre-surgical mapping (Black & Ronner, 1987; Lucas, McKhann, & Ojemann, 2004; Ojemann & Whitaker, 1978; Ojemann, 1983), and have been interpreted by some researchers as representing distinct cortical networks for processing different languages (K. H. Kim et al., 1997; Raboyeau et al., 2004, 2008, 2010). However, an alternate explanation for selective language disruption during invasive electrical stimulation is the higher spatial resolution for invasive electrical stimulation as compared to fMRI, that allows differentiation of smaller, language specific modules distributed within shared language processing regions (Abutalebi & Green, 2008). For example, invasive intracortical electrode mapping has shown that articulation of distinct phonemes occurs at very high resolution (3mm2; Blakely, Miller, Rao, Holmes, & Ojemann, 2008), with changes specific to different aspects of verbal memory encoding occurring at the level of the individual neuron (Ojemann, Schoenfield-McNeill, & Corina, 2009). Although researchers have speculated that within a shared substrate for language processing, small populations of neurons that are sensitive to the components of language and to different languages coexist in the same general region but may be differentiated at a finer level (Chee, Soon, & Lee, 2003; Indefrey, 2006; Klein, Zatorre, et al., 2006), such conclusions are difficult to make on the basis of functional imaging alone, which lacks the spatial resolution to study individual neurons.

3.2.4 EFFORTFUL LANGUAGE PROCESSING DURING L2 ACQUISITION

Several researchers have observed that language processing is more effortful in L2 than in L1 (Green, 1986; Perani et al., 2003; Raboyeau et al., 2008; Rudner & Rönnberg, 2008), reflecting challenges related to both phonological and semantic components of L2 processing. It has been observed that pronunciation of recently acquired words in an L2 requires additional articulatory effort than pronouncing well learned L1 words (Raboyeau et al., 2008), and that lexical difficulties often occur when choosing the appropriate L2 word during speech (Green, 1986; Rudner & Rönnberg, 2008). Effortful lexical retrieval owing to phonological and semantic limitations in an L2 may require additional attentional and working memory resources during language processing (Perani et al., 2003; Raboyeau et al., 2010; Rudner & Rönnberg, 2008), which may result in increased activity in regions of the prefrontal cortex (Green, 1986; Perani et al., 2003). This hypothesis has been supported in studies that have reported more extensive cortical activity associated with effortful lexical retrieval in L2 as compared to L1 (Briellmann et al., 2004; De Bleser et al., 2003; Golestani et al., 2006), or when distinguishing difficult compared to easy phonetic contrasts in an L2 (Callan et al., 2003) independent of age of L2 acquisition.

In a study of multi-lingual individuals who completed a verb generation task in four languages of varying proficiency, Briellmann and colleagues (2004) reported a significant negative relationship between level of proficiency and cortical activation. Specifically, language fluency was negatively correlated with brain activation in LH language regions, indicating that participants had greater brain activity for languages in which they produced fewer words per second during the respective verb generation task. The authors interpreted their findings as representing a common LH network that subserves multiple languages, with low proficiency languages recruiting a more extensive cortical network that includes both LH language regions as well as homologous RH regions (Briellmann et al., 2004).

Similar findings were reported in participants with good to very good proficiency in their L2, who had significantly more activity in dorsal and ventral left inferior frontal and temporo-parietal regions during covert L2 picture naming for non-cognates, but not for cognates, compared to L1. Additionally, non-cognate objects were named significantly less accurately than cognates or L1 words, indicating difficulty with lexical retrieval of non-cognates in L2. Based on these findings, the authors suggested that low proficiency bilingual processing requires extensions of the frontotemporal regions that are normally engaged for lexical retrieval (De Bleser et al., 2003).

In terms of phonological processing, in Japanese-English bilinguals, cortical activation for the difficult /r-l/ phonetic contrast was much more extensive than for the easy /b-g/ phonetic contrast relative to a signal corrected noise condition (Callan et al., 2003). Surprisingly, following one month of extensive feedback-based perceptual identification training of the /r-l/ contrast, activation for /r-l/ identification was even more extensive than pre-training in several LH and RH frontal and temporal regions including the insula and Broca's area (Callan et al., 2003). However, in addition to differences in phonology, words may have different grammatical properties in different languages that also have to be learned. For example whereas English words are gender neutral, words in Spanish have an associated gender and are often preceded by a gender specific pronoun such as *la* or *el.* Such differences in grammatical properties may influence the effort required during vocabulary acquisition and subsequent lexical retrieval.

3.2.5 THE CONVERGENCE HYPOTHESIS: A COMMON NEURAL CIRCUITRY

The convergence hypothesis (Green, 2003) suggests that acquisition of an L2 occurs within the developed neural system of L1. This hypothesis allows for some differences in cortical activation during the initial stages of L2 learning, which may require additional cognitive resources for effortful lexical retrieval (Abutalebi &

Chang-Smith, 2013). Consistent with the literature reviewed above (Briellmann et al., 2004; Chee, Tan, et al., 1999; Chee, Caplan, et al., 1999; De Bleser et al., 2003; Klein, Zatorre, et al., 2006; Klein et al., 1999; Perani et al., 2003), more extensive brain activity during L2 than L1 processing typically occurs primarily in the left prefrontal cortex, and these differences seem to disappear as L2 proficiency increases (See Abutalebi & Chang-Smith, 2013; Indefrey, 2006 for comprehsive reviews). Green (2003) suggested that as an L2 becomes more proficient, additional cognitive resources are no longer required and the neural representation of L2 converges to that of L1. Thus, the convergence hypothesis explains the more extensive pattern of cortical activation for L2 than L1 in low proficiency bilingual processing (Briellmann et al., 2004; De Bleser et al., 2003), as well as the similar profile of cortical activity that has been reported in high proficiency bilinguals for both L1 and L2 (Chee, Tan, et al., 1999; Chee, Caplan, et al., 1999; Klein, Zatorre, et al., 2006; Klein et al., 1999).

3.2.6 EFFORTFUL LEXICAL RETRIEVAL AND RIGHT HEMISPHERE ACTIVATION

Although current scholarship on cortical activity associated with L1 and L2 processing does not support the view that languages learned later in life involve more RH involvement than those learned early (Klein, Zatorre, et al., 2006; Klein et al., 1999; Vingerhoets et al., 2003; See for reviews Abutalebi & Chang-Smith, 2013; Indefrey, 2006), some researchers have suggested that RH language homologues may play a particular role during effortful lexical retrieval and articulation in low proficiency L2 learners (Raboyeau et al., 2004, 2008). Raboyeau et al. (2004)

studied cortical activity associated with picture naming in low proficiency French-English bilinguals who had learned English in school but not mastered it. During a picture-naming task involving the naming of monochromatic line drawings, participants scored on average 43.9/50 (SD = 4.8) for French, but only 3.2/50 (SD = 2.9) for English. A comparison of brain regions involved during these picture-naming tasks indicated that very low proficiency in English was associated with activation of an extensive RH network including frontal, temporal, subcortical, and cerebellar regions for English vs. French, whereas more extensive activation in LH fusiform gyrus, middle frontal, inferior and middle temporal regions was noted for French vs. English (Raboyeau et al., 2004).

In a subsequent study, Raboyeau et al. (2008) compared right inferior frontal activity in low proficiency L2 learners and in aphasic patients. It has been well documented that an increase in cortical activity in RH language homologues occurs during language processing following stroke damage to primary LH language regions (Karbe, Herholz, Weber-Luxenburger, Ghaemi, & Heiss, 1998; Karbe, Thiel, et al., 1998; Saur et al., 2006; Thiel et al., 2001; Winhuisen et al., 2005). One explanation for increased RH activity following LH damage is the functional recruitment hypothesis, which suggests that undamaged cortex in the contralateral hemisphere that is functionally connected to the speech network but not normally needed for language processing is recruited through an inter-hemispheric shift in language networks in order to compensate for aphasic impairment (Crinion & Price, 2005; Musso et al., 1999; Rosen et al., 2000; Saur et al., 2006; van Oers et al., 2010). In the study by Raboyeau et al. (2008), both aphasics and healthy controls participated in a lexical training program designed to assist with lexical retrieval of object names in the native language of aphasic patients, and in a previously learned but not mastered L2 for healthy controls. A comparison of cortical activity during picture naming tasks conducted post- vs. pre- lexical training in both groups revealed a similar pattern of activity increase in right frontal and insular regions that correlated with improved lexical retrieval. Accordingly, the authors concluded that enhanced RH activity both in recovering aphasics and L2 learners reflects functional recruitment of RH language homologues to compensate during language tasks that involve effortful lexical retrieval and articulatory processing (Raboyeau et al., 2008). However, the authors reported only results of a conjunction analysis, in which post-training naming was compared to pre-training naming, but not activity that was present during individual naming tasks at either time point for either group. Thus it is difficult to compare their results directly to those of previous studies involving L2 learners.

Extensive RH involvement during effortful lexical retrieval and articulation in low proficiency L2 learners raises questions as to whether abnormal levels of RH activity associated with L2 production represent an increased reliance on auditory attention and working memory for complex phonological and verbal material (Vigneau et al., 2011), or functional recruitment of additional cortex for effortful language processing, similar to that which may occur following a LH lesion (Raboyeau et al., 2008). To date we are aware of no studies that have examined cortical activity during the very earliest stages of L2 learning in adults with no prior L2 exposure. Although there is evidence to support the convergence of more extensive L2 than L1 cortical activation as L2 proficiency increases (e.g. Briellmann et al., 2004; Chee, Tan, et al., 1999; De Bleser et al., 2003; Klein, Zatorre, et al., 2006), this process has not been studied explicitly as most language studies do not involve longitudinal training of very early L2 acquisition in a single cohort. Thus, studying activation associated with L2 at various levels of proficiency and learning may be a suitable model for understanding the hypothesized process of convergence (Green, 2003) during the earliest stages of language assimilation.

3.2.7 THE PRESENT STUDY

The goal of the present study was to further our understanding of cortical activity associated with the effortful phonetic and semantic processing that occurs during the early stages of L2 learning. Our participants included unilingual English speaking individuals with no previous exposure to Spanish, who were taught Spanish words for the first time prior to completing English and Spanish picture naming tasks during an fMRI scan. We expected that naming pictures in English would represent a relatively automatic process whereas naming pictures using less familiar words in Spanish would be more effortful, providing a model of effortful language production in terms of both lexical retrieval and articulatory processing. As such, our hypotheses and results are presented in terms of automatic vs. effortful language production as opposed to representing equivalent tasks in an L1 and L2.

Based on previous findings of a single language network for both L1 and L2 processing (e.g. Chee, Tan, et al., 1999; Klein et al., 1999) combined with findings that low proficiency L2 speakers activated canonical LH language regions associated with phonological and semantic processing (Briellmann et al., 2004; De Bleser et al., 2003), we expect to see activity in classical language areas of the LH, including the IFG, at the group level during picture naming tasks in both languages. However, based on findings that very low proficiency in an L2 was associated with less extensive activation in LH language regions (Raboyeau et al., 2004), but more extensive activity in RH homologues (Briellmann et al., 2004; Raboyeau et al., 2004), we hypothesize that LH activity will be more extensive during English than Spanish naming; and that more activity will be seen in RH regions that are homologues of classical LH language regions during Spanish compared to English picture naming. We further hypothesize that picture naming in participants' native English will be more strongly associated with semantic processing, whereas Spanish, in which participants have very low proficiency and less familiarity with individual phonemes, will be more strongly associated with phonological processing. Accordingly, we expect that activity during English naming will be located within the ventral portion of the pars triangularis whereas activation for Spanish naming will be located within the pars opercularis and/or dorsal pars triangularis (Vigneau et al., 2006).

In addition to group level results, given the discrepant findings regarding spatial separation of peak activity for covert L1 and L2 language production at the individual level (K. H. Kim et al., 1997; Klein et al., 1999; Lucas et al., 2004), and subsequent suggestions that analyzing data at an individual level may further clarify group findings (Indefrey, 2006) and provide understanding of individual contributions to the group mean (Klein, Zatorre, et al., 2006), we analyzed individual activity within Broca's area and homologue during naming tasks. Based on our previously stated expectation that picture naming in English and in Spanish will activate a common language network overall, but rely on different components of language processing, we expect to see spatial separation of peak regions of activity that occur during English vs. Spanish naming tasks. We further expect that at the individual level, all participants will show some activity that is unique to both English and Spanish naming respectively, but also activity that is common to both naming tasks.

3.3 MATERIALS AND METHODS

3.3.1 PARTICIPANTS

Thirty-five healthy right-handed English-speaking participants (13 women, mean age 43.7, SD 10.6) with no known history of neurological or physiological disease and who were free from any contraindications to MRI were included in this study. All participants also participated in a previous study on second language acquisition. One participant's anatomical MRI evidenced an apparent structural abnormality and so this person's data were excluded from the study. For another participant, the data were corrupted on the MRI scanner and were unusable for group analysis. Thus, data from 33 participants (11 women) were used in the statistical analysis reported. Remaining participants had an average of 17 years of formal education (SD = 2.7), and all performed in the average to superior range on a number of working memory and processing speed tests including Trail Making Test A and B, Digit Symbol Coding from the WAIS-III, and Letter-Number Sequencing and

Spatial Span from the WMS-III. Participants were unilingual native English speakers with no previous training in Spanish. All participants gave informed consent to participate in this study, which was approved by the CDHA and IWK Research Ethics Boards.

3.3.2 GENERAL STUDY PROCEDURE

The present study was conducted over a two-day period in which participants learned novel Spanish vocabulary, participated in an fMRI scan, and completed a test of naming ability. Participants underwent two L2 training sessions using LANGA (LANguage GAming) software in which they were taught 24 Spanish words on each of two consecutive days. Immediately following the second LANGA session participants completed a structural and functional MRI scan. Following the MRI scan, all participants completed a test of Spanish naming ability.

3.3.3 LEXICAL TRAINING

LANGA is a set of games and animated tutorials co-developed by our lab and Copernicus Studios, Inc. of Halifax. In all the games, players were taught word-picture associations and then drilled on them through games, which required naming of those pictures. Naming accuracy was assessed by speech recognition algorithms (Telisma; Paris, France), and feedback on pronunciation accuracy was provided. Preliminary data from a pilot study in our lab using a previous version of LANGA in which players learned Spanish nouns suggested that most subjects could accurately name a high percentage of pictures of the words they were trained on after only 2 days of training. In pilot testing, 12 words per day were taught. In the present study participants learned 24 Spanish nouns and verbs each day, all of which were non-cognates (orthographically and phonologically dissimilar to their English translations). The reason for doubling the number of words taught per day was to increase the difficulty of the task, in order to create more inter-subject variance in performance. Spanish words consisted of the names of a mixture of natural and manufactured items, and verbs. These included 4 natural objects, 12 manufactured objects, 16 occupations, and 16 verbs.

3.3.4 STIMULI

During the MRI task, participants were shown pictures from the LANGA training program and asked to name the words that they had been learning in Spanish. Different stimuli, chosen from the Rossion-Pourtois Picture set (Rossion & Pourtois, 2004), a standardized set of 260 coloured line drawings, were used for the English naming task. English words consisted of 24 natural and 24 manufactured items. Although verbs were included in the Spanish set, we did not include them in the English set because without prior training, we felt that the association between a particular picture and a verb might be less obvious or consistent across participants than unambiguous objects. A list of words used during the English naming task is provided in Appendix B. All pictures were presented on a white background.

3.3.5 BEHAVIOURAL OUTCOME MEASURES

A naming test comprised of the same pictures that were used in the MRI task was completed by each participant post-MRI. Spanish words were scored on a 5-point likert scale ranging from 0 to 4 by a minimum of 2 independent raters (κ =

.75). A score of 4 points represented a perfect word score, 3 points a minor mispronunciation, 2 points were awarded for a word that was imperfect but recognizable as the target word and that had the same basic form and correct number of syllables, but with 1-2 phoneme errors or 1 stress error, 1 point was awarded for a word that resembled the target word but was clearly not correct (i.e. 3-4 phoneme errors, phoneme and stress errors combined, missing the end of a word etc.), and 0 points were awarded if the word said was not recognizable as the target word, substitution of an English word, or non-response. In the event of a discrepancy greater than one point the word was scored by a third party to reduce the discrepancy, improving inter rater reliability to κ = .81. Naming scores were averaged across raters and the resulting scores were used to obtain an overall level of Spanish naming ability.

To ensure that our participants were familiar with the English words, an English naming test was also completed by each participant. English words were scored on a 3-point likert scale ranging from 0 to 2 by a minimum of 2 independent raters (κ = .91). For English words, 2 points represented a perfect word score, 1 point an imperfect or partial, but recognizable word, and 0 points a word that had more than 2 phoneme errors, was incorrect, or a non-response. For both English and Spanish naming, if the participant named the picture in question with a related or reasonable word that was not the target word (i.e. rat vs. mouse), the response was deemed to represent verbal fluency in the target language and was considered correct for the purpose of this study and scored accordingly.

3.3.6 MRI DATA ACQUISITION

MRI scans were acquired using a GE 1.5 Signa Excite scanner. Functional MRI scans were acquired using a standard spiral-out pulse sequence with full brain coverage, TR = 2.2 sec, TE 40, flip angle 90, bandwith 125, FOV 24, slice thickness 4.5, 0 space frequency 64, 180 temporal frames. A high-resolution T1-weighted anatomical scan was acquired for each participant to aid in localization of activation. A T1-weighted structural scan was acquired from each participant using a SPGR pulse sequence with a 256 x 256 matrix, 186 slices, 1 mm isotropic resolution, TR = 11.3 s; TE = 4.2 ms; flip angle = 20 deg.

3.3.6.1 Functional MRI

The fMRI component of the study consisted of four runs, two each of Spanish naming and English naming, each lasting 6 minutes and 41 seconds. During each run, a blocked experimental design was used with five 30-second naming blocks, five 30-second control blocks, and seven 15-second rest blocks alternating in a randomized fashion. Stimuli were pictures that corresponded to the Spanish words on which the participants had trained, or novel pictures that were to be named in English, as well as scrambled images of the same pictures, used as a control condition. Stimuli were presented using Presentation software (Version 16.3, Build 12.20.12) and projected from an LCD projector onto a screen at the head of the bore of the MRI scanner that was visible through a mirror attached to the MRI head coil. All pictures were randomly assigned to naming blocks in groups of nine, with different combinations of pictures presented in each of the two Spanish and English scans. Both Spanish and English scans were counterbalanced across participants. In each naming block nine stimuli were presented for 3300 ms each, for a total of 45 stimuli in each run. An example of an MRI run is presented in Figure 3.1. Participants were instructed to try their best to name each picture in the language corresponding to each scan, even if they had retrieval difficulties. During active control blocks participants were instructed to verbalize the word 'picture' in response to scrambled images, in order to control for brain activation during lexical retrieval and articulation of well-learned words as well as for visual stimulation. Because it was not possible to record verbal responses during the scan due to the excessive noise created by the MRI, participants were instructed to press a button with their right or left hand as they made each verbal response in order to verify that a response was made. Rest blocks provided a passive baseline condition that involved simply staring at a fixation cross. Response hand was randomized across fMRI scan to avoid confounding activation associated with button pushing.

3.3.7 MRI DATA PREPROCESSING AND ANALYSIS

fMRI data processing was carried out using FEAT (fMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Prior to statistical analysis, the following preprocessing steps were applied to the data from each run, for each subject: motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002); non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 7.0 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; and high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 sec).

Statistical analysis proceeded through three levels. In the first level, each individual run was analyzed, using general linear modeling (GLM) (Woolrich, Ripley, Brady, & Smith, 2001). The time series representing the naming blocks for each language, and their respective active and passive control conditions were entered as separate regressors into the GLM, with prewhitening to correct for local autocorrelation. Coefficients were obtained for each stimulus type, for contrasts between each naming type and its scrambled image control condition, and between each naming type and rest condition.

The second-level analysis was performed for each participant, across runs, to identify brain areas activated by each naming condition relative to active and passive control conditions, and to compare activation between the two naming conditions (English and Spanish). Inputs were the contrast coefficients obtained from the first-level GLM analysis for the comparison of naming and control conditions. This was done using a fixed effects model, which forced the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004; Woolrich, 2008). Clusters were thresholded using Z > 2.3 and a corrected cluster significance threshold of *p* = .05 was used (Worsley, 2001).

A series of third-level analyses were then performed to obtain across-subjects results. These used the coefficients from each subject determined in the second-level GLM. These were done using FLAME (Woolrich et al., 2004) with Z (Gaussianized t-F) statistic thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = .05$ (Worsley, 2001). These allowed us to determine statistically significant levels of activity for English, Spanish, English-Spanish, and Spanish-English conditions. For each of these analyses, naming activity was calculated by subtracting activity during the control condition, and then masking this map with the naming minus rest contrast.

Active brain areas for all conditions were labeled using the Harvard-Oxford Cortical and Subcortical Structural Atlases (Desikan et al., 2006; Goldstein et al., 2007; Makris et al., 2006), and the Cerebellar Atlas in MNI152 space after normalization with FNIRT (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009), distributed with the FSL software package.

3.4 RESULTS

3.4.1 OUT OF SCANNER TESTING

Post-MRI Spanish naming performance varied considerably across participants, with a mean accuracy score of 83.35/192 (SD = 28.75). English naming was assessed as part of an alternate study using a time-limited test of English naming ability; mean accuracy was 80.92/96 (SD = 8.67). However, for the majority of participants an imperfect English naming score represented items that were missed due to speed rather than accuracy. On the words that were named in the time allotted, participants provided an acceptable response to the majority of items, with the exception that 11 participants were unable to name the picture of a spinning wheel and two participants were unable to name the picture of a peacock. Although participants at times substituted related or similar objects or animals for the picture to be named (i.e. rat for mouse, pheasant for peacock), all such responses were deemed reasonable and were considered to represent fluency in English naming during fMRI tasks.

3.4.2 FUNCTIONAL MRI RESULTS

The activation patterns associated with English or Spanish naming relative to the control conditions are shown in Figure 3.2. Both English and Spanish naming evoked left hemisphere activation in the inferior frontal gyrus pars triangularis and pars opercularis, the precentral gyrus, middle frontal gyrus, and the frontal opercular cortex ($p < .001$). Both languages also evoked bilateral activation in the lateral occipital cortex and the cerebellum ($p < .001$). Additionally, English (but not Spanish) naming evoked right hemisphere activation in the frontal pole, insula, and primary motor and sensory cortices in the pre- and post-central gyri ($p < .01$), as well as bilateral activation in the basal ganglia (head of the caudate nucleus and putamen) and thalamus ($p < .001$). The details of these activations are reported in Table 3.1.

As indicated by areas of disjunction in Figure 3.2, activation in right and left frontal regions was more extensive for English than for Spanish naming tasks. Statistical comparison between the two naming tasks supported this finding for both the right and left inferior frontal gyri (Figure 3.3). English naming elicited significantly greater activation than Spanish naming in right hemisphere pre- and post-central gyri ($p < .05$), the right temporal occipital fusiform cortex, lingual gyrus, and occipital pole ($p < .01$), the left insula, thalamus, putamen, pallidum and hippocampus ($p < .001$), and subcortically in the right thalamus, caudate, putamen, and hippocampus ($p < .05$). In contrast, Spanish naming elicited significantly greater activation than English naming in middle and bilateral cerebellar regions ($p < .01$), and right parietal regions ($p < .05$). Details of the differences between conditions are provided in Table 3.2.

3.4.3 SPANISH NAMING ACCURACY AS A COVARIATE

To explore any possible influence that Spanish naming accuracy may have had on brain activation, accuracy scores obtained during a post-MRI Spanish naming test were included as a covariate. Consistent with the results reported above for Spanish naming, independent of Spanish naming accuracy, participants reliably activated the left IFG pars opercularis and pars triangularis (Brodmann areas 44 and 45), precentral, and middle frontal gyri, and lateral occipital cortex during Spanish naming ($p < .001$). In addition to the results obtained for Spanish naming in the main analysis, the Vermis V1 was active independent of Spanish naming accuracy ($p < .001$; See Figure 3.4). Activation that was not present in the main analysis, but that correlated directly with naming accuracy was found at trend levels ($p < .01$, uncorrected) in the right frontal pole and anterior cingulate. Results of the covariate analysis are presented in Table 3.3.

3.4.4 INDIVIDUAL fMRI ANALYSIS

To determine whether English and Spanish naming preferentially activated different regions within Broca's area, MNI coordinates of the peak region of activation were identified for English and for Spanish naming in BA44 and BA45 in both hemispheres using the Juelich Histological Atlas (Eickhoff et al., 2005, 2007; Eickhoff, Heim, Zilles, & Amunts, 2006). Regions of interest are presented in Figure 3.5. The total number of active voxels within each of these regions was also identified and compared across languages in order to determine whether differences existed in the proportion of unique or overlapping voxels in each language or in the extent of activation for English and Spanish. Across our sample, 15 participants had activation in BA44 of the LH, three participants had activation in BA44 of the RH, ten participants had activation in BA 45 of the LH, and five participants had activation in BA45 of the RH for both English and Spanish naming. Analyses were run in R 3.1.0 using linear mixed effects with the lme4 package, v 1.1-6. Statistical results for these analyses are presented in Table 3.4.

Firstly, we compared the Euclidian distance between peak activation coordinates for English and Spanish within each ROI for each participant. We found significant differences in the spatial location of the peak activation for English and Spanish naming activity in BA44 and BA45 in both hemispheres (See Table 3.4).

Secondly, the raw number of voxels that had activity that was unique to English, unique to Spanish, or that had activity common to both languages (overlap) was compared in BA44 and BA45 of each hemisphere (See Figure 3.6). In BA44, linear mixed effects analysis revealed a main effect of condition F(2, 357) = 6.22, $p < .01$, indicating that more voxels had unique than overlapping activity, and a main effect of hemisphere F(1, 357) = 53.05, $p < .001$, which was due to a greater number of voxels that were active in the LH compared to the RH. The interaction between condition and hemisphere was also significant F(2, 357) = 5.67, $p < .01$. A series of post-hoc t-tests revealed significant differences between the proportion of unique vs. overlapping voxels for Spanish naming in the LH, with more voxels unique to Spanish than to English, t(357) = 2.88, $p = .004$, and more unique to Spanish than overlapping voxels that were active for both languages, t(357) = 4.00, $p < .001$. In contrast, in the RH there were more voxels unique to English naming than overlapped for both languages, t(357) = 2.53, $p = .012$ (See Table 3.4).

Similar results were noted in BA45, with main effects of condition F(2, 357) = 4.68, $p < .01$, due to more voxels with unique than overlapping activity; and hemisphere F(1, 357) = 32.95, $p < .001$, due to more active voxels in the LH than RH. However, the interaction between condition and hemisphere was only marginally significant F(2, 357) = 2.66, $p = .07$. Post hoc t-tests revealed significant differences between the proportion of unique vs. overlapping voxels for Spanish, with more voxels unique to Spanish than English, t(357) = 2.08, $p = .04$, and overlap t(357) = 3.39, $p < .001$ (See Table 3.4). In all cases for both BA44 and BA45, there was a greater number of active voxels in the LH than in the RH.

Finally we examined the mean number of active voxels in each ROI for each language across participants. No statistically significant differences were found for mean number of voxels activated during Spanish or English naming in either BA44, BA45 or Broca's area in either hemisphere (See Figure 3.6).

3.5 DISCUSSION

The purpose of this study was to contribute to the literature on cortical activity associated with effortful lexical retrieval and articulation of words in an unmastered L2. Participants learned novel Spanish words prior to participating in an overt picture-naming task during fMRI scanning to determine which regions of the brain were active during lexical retrieval of newly acquired words or words in one's native language.

Consistent with our first hypothesis that both English and Spanish naming would activate classical LH language regions, picture naming in both English and Spanish was associated with activation in left anterior frontal regions traditionally associated with language production, including the IFG pars triangularis (BA45) and opercularis (BA44). The left IFG has been consistently associated with both phonological and semantic processing in first and subsequent languages (Indefrey & Levelt, 2004; Klein et al., 1994; Papoutsi et al., 2009; Perani et al., 1998; Raboyeau et al., 2010). Beyond primary language regions, both English and Spanish activated regions of the visual cortex including the lateral occipital cortex bilaterally and the right temporal occipital fusiform cortex. These regions are consistent with the posterior multimodal and heteromodal association cortex, typically associated with visual object processing but which Binder and colleagues included as one of the three broad regions commonly activated during semantic processing (Binder et al., 2009).

Our hypothesis that English naming would activate the ventral portion of the pars triangularis whereas Spanish naming would activate the pars opercularis and/or dorsal pars triangularis was likewise supported. Indeed Spanish naming was associated with activity in both the pars opercularis and the dorsal pars triangularis, whereas English naming was associated with activity in the ventral portion of the pars triangularis as well as a more extensive network of regions associated with phonological and semantic processing including the pars orbitalis and ventral pars opercularis (Vigneau et al., 2006). These findings are consistent with our expectation that effortful lexical retrieval and articulatory processing was associated more strongly with phonological than semantic processing. This distinction is highlighted in the contrast condition, in which English naming showed greater activity in the ventral pars triangularis and the pars orbitalis when compared to activity for Spanish naming.

Our hypothesis that English naming would be associated with more extensive LH activity, but less extensive RH activity than Spanish naming was only partially supported. Whereas English naming was associated with activity in both the LH and the RH, Spanish naming was associated with activity in the LH only. In fact, results of our study revealed more extensive activity in both the LH and the RH during English as compared to Spanish picture naming.

3.5.1 ENGLISH VS. SPANISH CONTRAST

A comparison of activity during English vs. Spanish naming tasks revealed a more extensive network for English than for Spanish picture naming, with increased activity in RH language homologues (posterior superior temporal and supramarginal gyri and planum temporale), the insula, pre- and post-central gyri (BA1/3a/4a/6), as well as subcortical structures including the thalamus, amygdala and hippocampus bilaterally, and the right striatum. This more extensive activation in English than Spanish may reflect both activation of a wider semantic network during lexical retrieval, as well as the additional verbal output that we expect occurred during the English naming blocks. Whereas the majority of pictures in the English naming condition were named correctly for all participants, post-MRI testing indicated a high non-response rate for the Spanish naming condition. Furthermore, although the portion of the left precentral gyrus associated with mouth and laryngeal motor function during phonation and articulation (Brown et al., 2009; Vigneau et al., 2006) was active during both English and Spanish naming tasks, RH homotopic representations of the larynx and tongue were more strongly associated with English naming. Thus, English naming likely involved greater facial muscle movement and articulation than Spanish naming. Also, whereas Spanish words had been learned and reviewed in a session immediately preceding the fMRI scan, the English words had not been rehearsed, and the images used to elicit the naming had not been previously viewed. Thus, increased activity in the insula and striatum may reflect stimulus novelty in the English naming task (Indefrey & Levelt, 2004).

3.5.2 SPANISH VS. ENGLISH CONTRAST

In contrast to previous research that has demonstrated a more extensive network of activation for L2 than for L1 (Briellmann et al., 2004; De Bleser et al., 2003; Wartenburger et al., 2003; See Abutalebi, 2008 and Indefrey, 2006 for reviews), Spanish naming did not elicit a more extensive network in frontal and prefrontal regions than English in either the LH or the RH in our participants. Rather, our Spanish minus English contrast revealed more extensive activation in lobules V and VI of the cerebellum bilaterally. Lobule VI of the cerebellum has been associated with orofacial functioning such as lip and tongue movement and vocalization (Brown et al., 2009; Grodd, Hülsmann, Lotze, Wildgruber, & Erb, 2001), and lobules V and VI of the cerebellum have been implicated in language and verbal working memory (Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997; Stoodley & Schmahmann, 2009), articulatory rehearsal (S. H. A. Chen & Desmond, 2005; Koelsch et al., 2009), and explicit memory retrieval (Desmond & Fiez, 1998). The cerebellum has also been identified as playing a role in somatosensory feedback during speech production (Hocking, McMahon, & de Zubicaray, 2008; Stoodley & Schmahmann, 2009). Klein, Watkins et al., (2006) documented increased cerebellar activity with increased articulatory complexity and number of syllables in nonword conditions in L2 compared to L1. The authors interpreted these findings as implicating a cortico-cerebellar system that has been previously associated with motor learning (Doyon, Penhune, & Ungerleider, 2003) in the learning of novel phonological sequences that are complex (Klein, Watkins, et al., 2006). Similar findings and conclusions have been reported by Callan et al. (2003), who reported cerebellar activity during the learning of a difficult phonetic contrast and suggested that the cerebellum may play a particular role in phonetic discrimination in an unmastered language.

In the present study, words in the Spanish naming task had, on average, a greater number of syllables (Mean = 3.40, SD = 1.05) than words in the English naming task (Mean = 2.10, SD = 0.93; t(94) = 6.40, $p < .001$). Spanish words were also more phonologically complex than the words in the English version of the task, as the Spanish words contained a number of phonemes not used in English (e.g., words that contained the *ñ* and *ll*). Thus, we would argue that increased cerebellar activity during the Spanish naming task reflects both increased speech motor control over phonological complexity of language, as well as an increase in verbal working memory and explicit recall of recently learned information.

However, although the cerebellar activity found in the Spanish minus English contrast in the present study is remarkably similar to that reported by Klein and colleagues, our findings are limited as our functional imaging scans did not include full coverage of the cerebellum in all participants. Although the activity we report in lobules V and VI does represent coverage for all participants, we are unable to draw conclusions regarding the presence or absence of activity in other portions of the cerebellum during English or Spanish naming. Future research that ensures adequate coverage of the cerebellum in all participants would serve to further clarify the role of the cerebellum in effortful articulatory processes and cognitive control of language processing.

3.5.3 PATTERNS OF ACTIVATION ACROSS PROFICIENCY LEVELS

Although a number of studies that have investigated language processing in late L2 learners have shown more extensive activity for L2 than L1 (Briellmann et al., 2004; De Bleser et al., 2003; Vingerhoets et al., 2003; Wartenburger et al., 2003; See Abutalebi, 2008 and Indefrey, 2006 for reviews), our participants showed less overall activation associated with newly learned words in Spanish than for well-known English words. However, in contrast to previous studies our participants had such low Spanish proficiency that the act of naming pictures using very novel vocabulary was likely not sufficient to activate the full language network. Given the high level of activity during L2 non-cognate naming compared to L1 naming reported by Raboyeau et al. (2010), we suspect that a certain level of L2 proficiency must be reached before the full language processing network, including RH regions, becomes involved in language processing. For example, Hartwigsen et al. (2013) found a prominent role for the left, but not the right posterior IFG during pseudoword repetition, suggesting that the right posterior IFG does not contribute to articulation of verbal stimuli that is not meaningful. Likewise, Wang and colleagues reported that subjects that had only minor exposure to and low overall proficiency in Chinese demonstrated some activity in Broca's area (BA44/45) during a Mandarin tone identification task, but no activity in Broca's homologue (Wang, Sereno, Jongman, & Hirsch, 2003). However, after a series of eight, 40-minute sessions in which subjects received auditory training to identify the tones, they demonstrated an emergence of activity in BA44 of the RH as well as more extensive LH language regions, including the superior and middle temporal gyri

(BA22). The increase in bilateral language-related activity with training supports the existence of an earlier stage of L2 learning that precedes the enrichment plasticity associated with more extensive activation of language circuitry in low proficiency L2 speakers.

Thus, we argue that very early in the process of L2 acquisition—before strong associations between novel phonological patterns and semantic and syntactic (lemma) representations have been established— L2 production may be more similar to pseudoword or artificial grammar production than to that of the moderate or high proficiency L2 speakers cited in much of the research. We argue that during this initial learning stage, learners are unable to engage the full language circuitry, and rely more heavily on cerebellar networks supporting verbal working memory, and complex articulatory processing.

3.5.4 SPANISH PROFICIENCY AS A COVARIATE OF NAMING ACTIVITY

This hypothesis is supported by an analysis of Spanish naming score as a covariate of naming activity in our participants. We found that irrespective of how successfully participants were able to reproduce the new Spanish words that they learned, participants reliably activated the left IFG (BA44/45) and parts of the precentral gyrus during Spanish naming blocks. This finding supports the importance of the role of Broca's area in motor speech output, regardless of language or level of proficiency. Additionally, across our participants there is a trend towards increased activation in regions associated with L2 processing and cognitive control with increased L2 proficiency. Activity that correlated with Spanish naming score was found at trend levels (*p* < .01, uncorrected) in the right frontal pole and the anterior cingulate bilaterally. The anterior cingulate has been associated with monitoring of competition among alternative verbal responses (Barch, Braver, Sabb, & Noll, 2000; Milham & Banich, 2005); and previous research has reported a correlation between activity in the anterior cingulate and improved lexical retrieval during L2 acquisition (Newman-Norlund, Frey, Petitto, & Grafton, 2006; Raboyeau et al., 2008).

3.5.5 VARIABILITY IN PEAK ACTIVATION DURING ENGLISH AND SPANISH NAMING

Consistent with our hypothesis that the participants in our study would show spatial separation in peak activity during English and Spanish naming tasks, we found a significant difference between the spatial location of peak activation of English and Spanish naming in both BA44 and BA45 in both hemispheres, and regions that were both unique to English and Spanish and that had overlap between the two languages. This finding is consistent with previous research that has reported distinct focal activations during covert sentence generation tasks in L1 and L2 (Golestani et al., 2006; K. H. Kim et al., 1997), with larger spatial separation reported for non-proficient (Golestani et al., 2006) or late L2 learners (K. H. Kim et al., 1997). Such separation in peak activity has been interpreted as representing distinct cortical representations for L1 and L2 processing within a common language network. However, research on proficient bilinguals failed to find spatial separation between L1 and L2 activation during a covert verb generation task (Klein et al., 1999). Furthermore, neither Kim et al. (1997) nor Golestani et al. (2006)

controlled for differences across grammatical structure or production volume of the languages included in their studies, which may have contributed to differences in syntactical processing or lexical retrieval across conditions. As well, Golestani et al. (2006) reported finding greater separation for low vs. high proficiency bilinguals, which may reflect a greater contribution of phonological vs. semantic processing to language production. We argue that in the present study, a similar difference between semantic and phonemic fluency in English as compared to Spanish picture naming accounts for the spatial separation in peak activity between the two conditions.

Given the very low proficiency level of our participants and the inherent differences in task difficulty between the English and Spanish naming tasks in our study, differences in cortical activity may in part be driven by articulatory difficulties (Klein et al., 1994), differential number of verbal utterances or muscle movement, low semantic knowledge, or differential inhibition of language (Paradis, 1996) rather than distinct neural circuitry that is language specific. It has been suggested that complex neural networks may be activated differentially by single words, and more complex networks may be activated by more complex tasks even within a single language (Posner & Pavese, 1998). In the present study, participants likely expressed more words in English and with greater facility than words in Spanish as the Spanish naming task was more difficult, and the words contained a greater number of syllables on average than the English task. Moreover, whereas language processes are expressed in milliseconds, the time required by fMRI to record cortical BOLD activity is expressed in seconds (Fabbro, 2001), and language tasks generally activate several cortical areas simultaneously. Thus, it is impossible to conclude definitively that the separation of peak areas of activation during language production in L1 and L2 reflects a difference that is specific only to language without considering level of task difficulty or cognitive load. In fact, the dichotomy of shared vs. separate systems for language processing in general is very likely an oversimplification of an incredibly complex system. For example, Chee and colleagues (Chee, Hon, Lee, & Soon, 2001; Chee et al., 2003) have demonstrated that whereas there appears to be a shared semantic system across languages, there are differences that occur at the lexical level; and neuronal networks that are sensitive to phonology, semantics, syntax, and language respectively likely coexist within a broader network of language regions within the frontal, temporal, and parietal lobes (Abutalebi & Green, 2008; Blakely et al., 2008; Chee et al., 2003; Indefrey, 2006; Klein, Zatorre, et al., 2006; Ojemann et al., 2009).

3.5.6 LIMITATIONS

The MRI task in the present study involved overt, rather than covert speech, which has the potential to produce head motion artifacts which may contaminate fMRI pictures (Bookheimer, 2002). Although our participants were instructed to move only their mouths, and practiced speaking without moving their heads prior to entering the MRI, this remains a potential limitation.

In the present study, only words that were both non-cognates and that were deemed unlikely to have been encountered by individuals with no formal Spanish training (i.e. el hechicero, sacude) were included in our LANGA protocol. However, based on post-MRI naming tests, our Spanish naming task proved very difficult for the majority of our participants, resulting in a high non-response or error rate. As well, in our Spanish training sessions and subsequent naming tasks, each Spanish noun was preceded by its corresponding pronoun (el or la), thus potentially increasing the level of difficulty level of the Spanish task, as well as introducing a grammatical component that was not possible to duplicate in the English naming task. Given that there are fewer multisyllabic English than Spanish words that can be pictorially depicted, words in the Spanish naming task had a greater number of syllables on average than words in the English naming task. Thus, differences between L1 and L2 naming may reflect differential recruitment of cortical regions that are more heavily dependent on syntax owing to the fact that the English and Spanish naming tasks were not equivalent. However, considering that the goal of the present study was to compare effortful lexical retrieval and articulation processing to automatic native language processing, these differences should not prevent conclusions to that effect.

Finally, although we were unable to control for naming accuracy during the fMRI scan, all participants were administered post-MRI naming tests to determine level of proficiency. However, we were unable to control for cortical activity reflecting correct, incorrect, or non-response items, as the noise level during fMRI tasks did not permit recording of verbal responses. Furthermore, while listening to recordings of the post-MRI Spanish naming task, it was clear that some participants said English words while trying to think of the Spanish counterpart, therefore, Spanish naming contrasted with English naming may not be a pure measure of differential language functioning. However, even incorrect or non-responses are likely to represent effortful lexical retrieval, as participants confirmed that they did put forth their best effort during the Spanish naming task as requested.

3.5.7 FUTURE WORK

Beyond group comparison of cortical activity associated with L1 and L2 processing, the present study investigated individual contributions to the group mean as recommended by Klein, Zatorre et al. (2006). However, those authors further recommend analyzing how individual levels of proficiency and L2 exposure may affect the haemodynamic response to language tasks. It is important to note that in the present study, despite individual variability in proficiency, all participants had approximately the same level of L2 exposure (two, one-hour training sessions). Future studies that examine cortical functioning at both the individual and group levels across a wide variety of proficiency levels will also be important to further clarify the issue of brain regions involved in first and second language processing. More specifically, additional levels of exposure and proficiency across subjects may serve to clarify not only the process of language acquisition, but also the mechanism by which language is acquired.

3.5.8 CONCLUSIONS

Collectively, our findings support a unitary general language-processing network in which L2 acquisition occurs within the developed neural system of L1. However, we propose an early component of language acquisition, involving a cerebellar network that supports verbal working memory and complex articulatory processing – before the L2 can be meaningfully assimilated – which precedes the enrichment plasticity associated with more extensive activation of language circuitry as L2 learners gain facility in the new language.

Table 3.1.

Location, spatial extent, and maximum z values in anatomically defined regions of interest (ROIs) of activity during English and Spanish naming.

		English					Spanish				
ROI	Hemi	*X*	*Y*	*Z*	Max z	Vol (ml)	*X*	*Y*	*Z*	Max z	Vol (ml)
Frontal Pole	L										
	R	34	34	-14	3.95	19.17					
		32	34	-8	3.83	19.17					
		38	54	-8	3.20	19.17					
		32	42	8	3.09	19.17					
Frontal orbital cortex	L	-44	24	-6	5.67	86.70					
	R										
Insular cortex	L										
	R	36	22	0	3.25	19.17					
IFG pars triangularis	L	-44	28	-8	5.67	86.70	-46	32	14	4.50	33.09
	R										
IFG pars opercularis	L	-50	12	20	2.14	86.70	-48	14	16	6.43	33.09
							-46	16	10	5.92	33.09
	R										
Putamen	L										
	R	20	12	2	4.74	19.17					
Middle frontal gyrus	L	-46	12	32	5.32	86.70					
	R	60	24	30	3.78	11.48					
Precentral gyrus	L	-42	2	32	5.42	86.70	-42	4	38	4.22	33.09
		-48	6	28	5.36	86.70	-48	4	46	4.05	33.09
	R	54	-6	38	4.00	11.48					
		46	-12	46	3.87	11.48					
		46	-8	58	3.71	11.48					
Postcentral gyrus	L										
	R	68	-8	18	4.01	11.48					
Inferior temporal gyrus	L	-44	-52	-14	7.09	122.02					
	R										
Temporal occipital fusiform cortex	L										
	R	28	-58	-14	8.06	122.02	38	-58	-8	6.15	65.73
		36	-48	-16	7.58	122.02					
Occipital fusiform gyrus	L										

		English						Spanish				
ROI	Hemi	*X*	*Y*	*Z*	Max z	Vol (ml)		*X*	*Y*	*Z*	Max z	Vol (ml)
	R							30	-62	-22	6.44	65.73
Lateral occipital cortex	L	-42	-72	-6	8.32	122.02		-40	-74	-6	6.69	65.73
		-36	-76	12	7.14	122.02						
	R	40	-68	-10	8.17	122.02		36	-74	0	7.14	65.73
Total volume						239.37						98.82

Note. IFG, inferior frontal gyrus; Hemi, hemisphere; R, right; L, left; Vol, volume. It should be noted that large clusters of activity seen in the figures overlap with several brain regions defined in this table. For each condition relative to its control condition, z maps were thresholded at Z < 2.3, with a corrected cluster size threshold of p = .05 prior to clustering within ROIs.

Table 3.2.

Location, spatial extent, and maximum z values in anatomically defined regions that showed significant differences between naming conditions.

		English > Spanish					Spanish > English				
ROI	Hemi	*X*	*Y*	*Z*	Max z	Vol (ml)	*X*	*Y*	*Z*	Max z	Vol (ml)
Precentral gyrus	L	-58	-2	12	4.54	19.22					
	R	52	-4	34	4.36	6.72					
		52	-4	26	4.21	6.72					
Postcentral gyrus	L										
	R	44	-16	46	5.70	6.72					
		50	-12	52	4.78	6.72					
		64	-10	18	3.67	6.72					
Central opercular cortex	L	-42	-10	16	5.26	19.22					
	R										
Superior temporal gyrus	L										
	R	46	-32	-8	4.42	4.97					
Supramarginal gyrus	L										
	R	50	-38	16	3.47	4.97					
Lingual gyrus	L										
	R	26	-54	-8	5.49	9.27					
Temporal occipital fusiform cortex	L	-28	-62	-8	5.96	44.20					
		-26	-56	-10	5.88	44.20					
		-24	-46	-16	5.85	44.20					
	R	28	-40	-16	5.92	9.27					
Occipital fusiform gyrus	L										
	R	22	-70	-8	3.82	9.27					
Occipital pole	L										
	R	22	-90	34	6.24	44.20					
		12	-94	30	5.09	44.20					
		22	-94	22	5.07	44.20					
	R	28	-2	6	3.89	6.70					
		26	-6	6	3.69	6.70					
Caudate	L										
	R	10	2	10	3.49	6.70					
Thalamus	L	-14	-24	-2	4.83	19.22					

		English > Spanish					Spanish > English				
ROI	Hemi	*X*	*Y*	*Z*	Max z	Vol (ml)	*X*	*Y*	*Z*	Max z	Vol (ml)
	R	14	-14	16	3.47	6.70					
		10	-4	12	3.17	6.70					
		14	-32	2	4.74	4.97					
Hippocampus	L										
	R	30	-32	-8	4.42	4.97					
Cerebellum V	L						0	-58	-16	4.03	8.26
	R										
Cerebellum VI	L						-8	-62	-24	3.81	8.26
							-20	-58	-26	3.81	8.26
							-14	-60	-24	3.80	8.26
	R						22	-60	-24	3.69	8.26
							24	-56	-26	3.68	8.26
Subcortical white Matter	L										
	R						22	-54	32	4.34	4.72
							28	-46	8	3.82	4.72
							22	-44	18	3.70	4.72
							34	-44	4	3.53	4.72
Total volume						91.08					12.98

Note. Hemi, hemisphere; R, right; L, left. It should be noted that large clusters of activity seen in the figures overlap with several brain regions defined in this table. Comparisons between naming conditions were performed by first subtracting the control condition from its respective naming condition, then thresholding at Z < 2.3, with a corrected cluster size threshold of *p* = .05.

Table 3.3.

Covariate analysis of regions that were active during Spanish naming independent of accuracy, and activation that correlated with Spanish naming accuracy at sub-threshold levels ($p < .01$, uncorrected).

		Independent of Accuracy					Correlated with Accuracy				
ROI	Hemi	*X*	*Y*	*Z*	Max z	Vol (ml)	*X*	*Y*	*Z*	Max z	Vol (ml)
IFG pars opercularis	L	-46	20	6	5.26	19.07					
		-46	14	22	3.99	19.07					
		-46	14	16	3.90	19.07					
	R										
Precentral gyrus	L	-48	4	44	3.25	19.07					
		-44	0	40	3.20	19.07					
	R										
Middle frontal gyrus	L	-38	26	22	3.03	19.07					
	R										
Frontal pole	L										
	R						52	46	0	2.9	
Anterior Cingulate	L						-2	30	-4	2.68	
	R						4	34	-4	2.67	
Pallidum	L						-14	0	-4	2.65	
	R										
Angular gyrus	L						-50	-52	22	2.95	
	R										
Occipital Pole	L										
	R						10	-102	14	2.98	
Lateral occipital cortex	L										
	R	40	-74	-2	4.98	25.66					
		56	-76	-4	4.92	25.66					
		50	-72	0	4.44	25.66					
		38	-64	8	3.81	25.66					
Cerebellum VI	L										
	R	4	-74	-	4.06	25.66					
		0	-78	20	4.02	25.66					
				-20							
Total volume						44.73					N/A

Note. IFG, inferior frontal gyrus; Hemi, hemisphere; R, right; L, left; Vol, volume. It should be noted that large clusters of activity seen in the figures overlap with several brain regions defined in this table. Location, spatial extent, and maximum z values in anatomically defined regions that showed significant activation during Spanish naming independent of naming accuracy, thresholded at Z < 2.3, with a corrected cluster size threshold of p = .05. Regions that correlated with Spanish naming accuracy were significant only at marginally significant levels, thresholded at Z < 2.3, with no cluster size threshold applied.

Table 3.4.

Differences in spatial location for peak activity during Spanish and English picture naming (peak to peak), and results of a comparison of the proportion of active voxels that were unique to English, unique to Spanish, or that were active during naming in both languages (overlap).

	LH		RH	
	t	*p*	t	*p*
BA 44				
Peak to Peak	7.43**	<.001	9.03**	<.001
English vs. Overlap	1.11	.266	2.53*	.012
Spanish vs. Overlap	4.00**	<.001	0.77	.441
English vs. Spanish	2.88**	.004	1.76	.079
BA 45				
Peak to Peak	10.16**	<.001	5.08**	<.001
English vs. Overlap	1.30	.193	1.73	.085
Spanish vs. Overlap	3.39**	<.001	0.83	.425
English vs. Spanish	2.08*	.038	0.93	.355
Broca's Area				
Peak to Peak	7.76**	<.001	9.42**	<.001
English vs. Overlap	1.28	.201	2.27*	.024
Spanish vs. Overlap	3.93**	<.001	0.83	.405
English vs. Spanish	2.65**	.008	1.44	.150

Note. BA44 and BA45 were identified in both hemispheres using the Juelich Histological Atlas (Eickhoff et al., 2005, 2007, 2006).

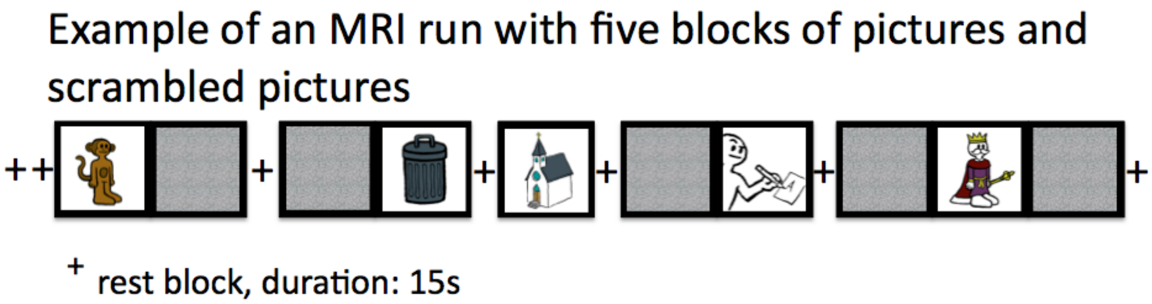

Figure 3.1. Example of an MRI run for both Spanish and English picture naming. Each run began with a rest block and was followed by 5 picture naming, 5 scrambled, and 4 additional rest blocks that were presented in a randomized order, followed by a final rest block. Pictures shown are from a Spanish naming run.

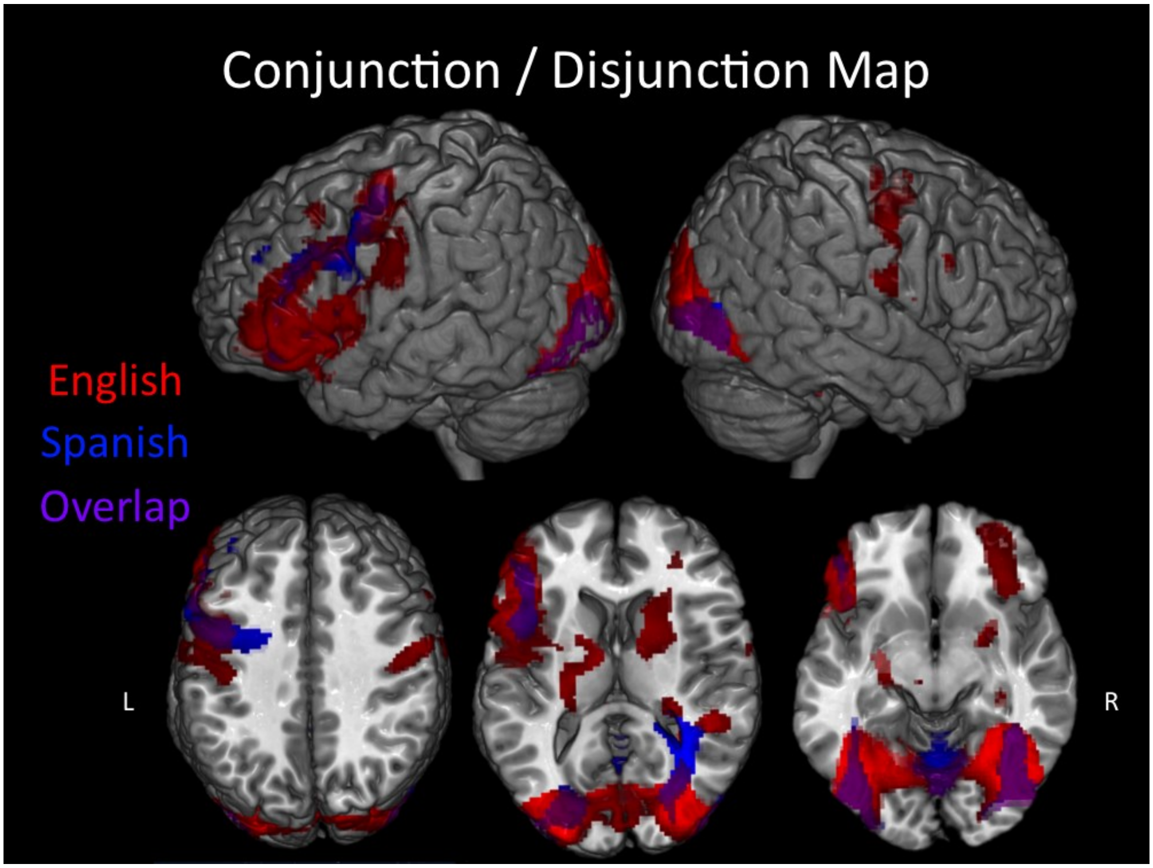

Figure 3.2. Activation elicited by each type of naming task relative to its matched control condition (scrambled images). Z statistic images were thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of *p* = .05. The maps for each condition have been overlaid to show areas of conjunction (i.e., significant activation for both English and Spanish naming) in purple and areas of disjunction in blue (activation for Spanish naming only) and red (activation for English naming only).

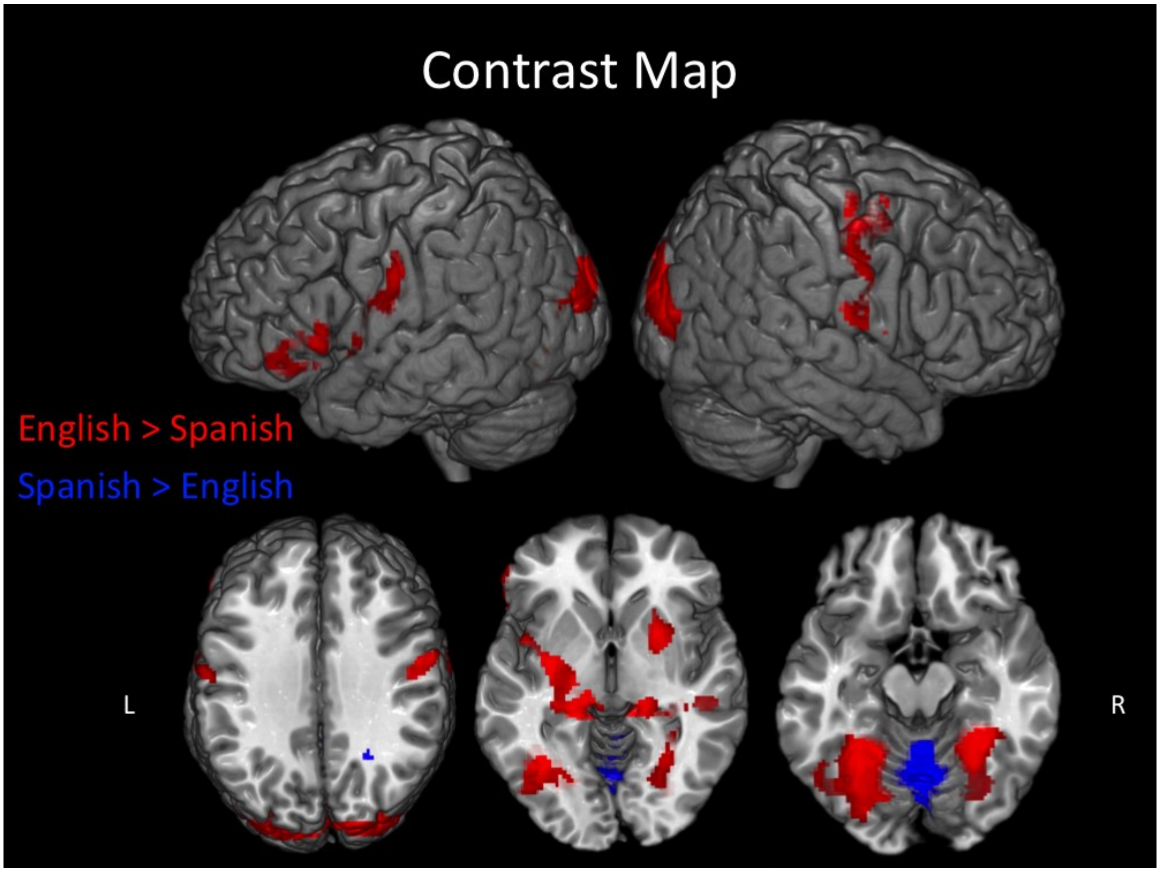

Figure 3.3. Areas of greater activation for English than Spanish (red) naming, and for Spanish than English (blue) naming. Z statistic images were thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of p = .05.

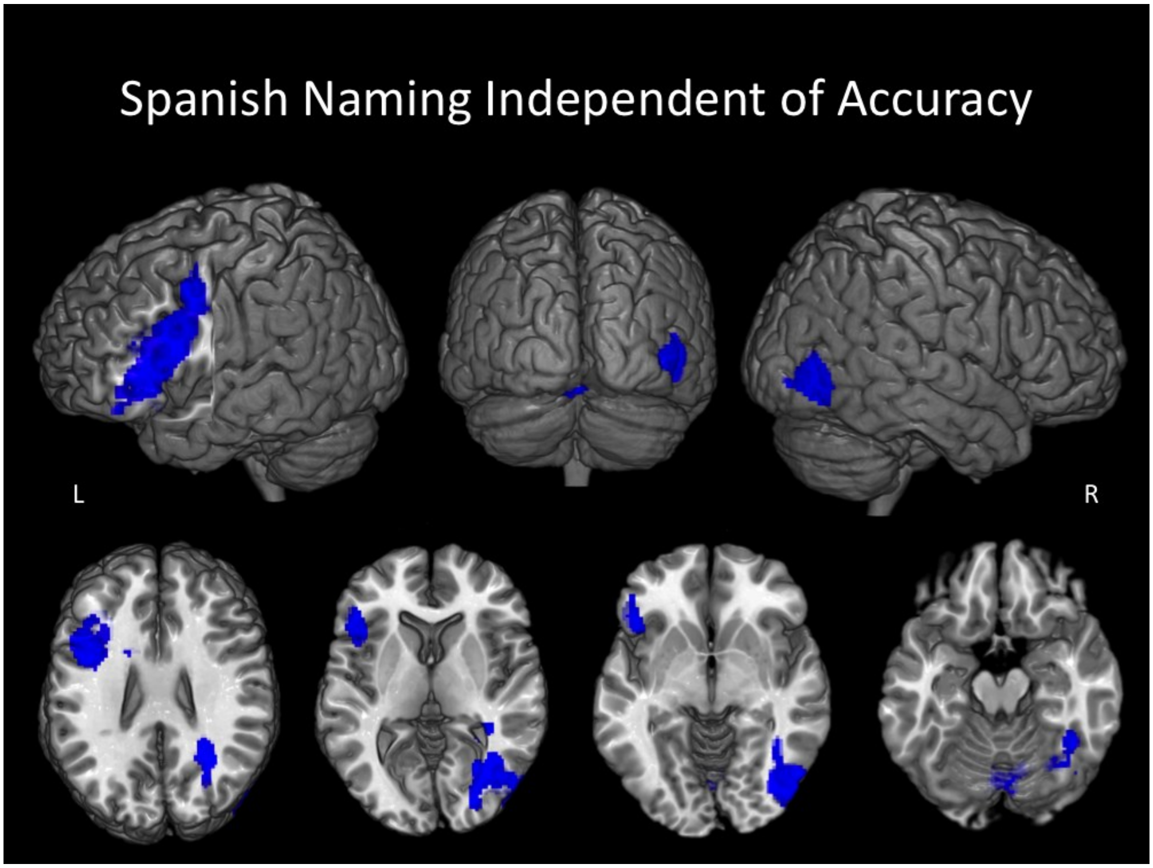

Figure 3.4. Spanish naming accuracy as a covariate of activity during Spanish picture naming. Activity represents regions that showed activity independent of naming accuracy.

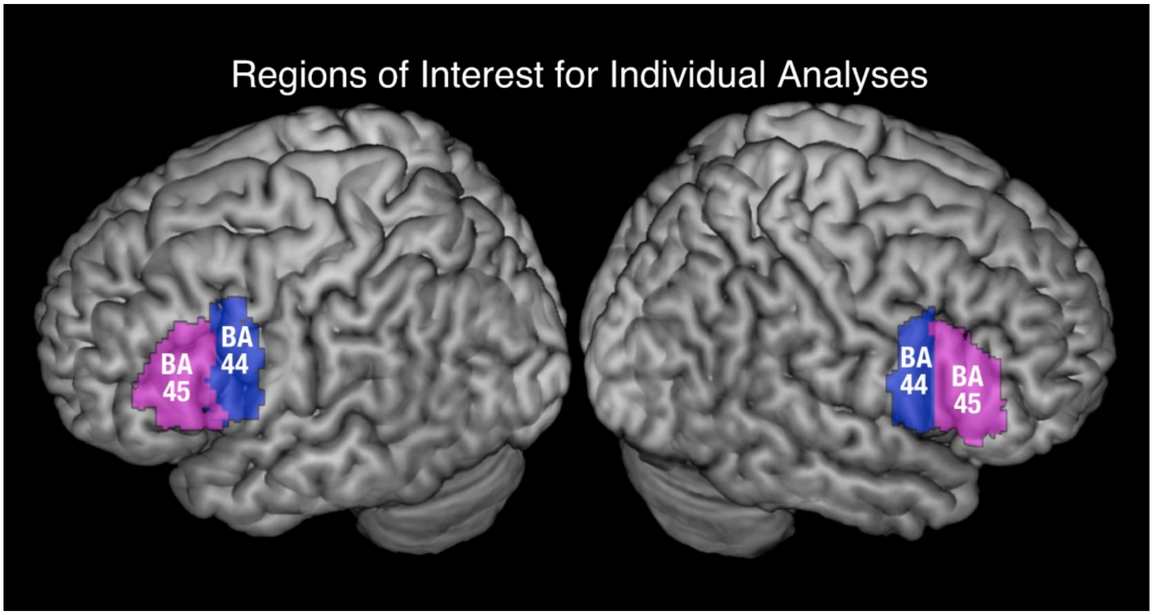

Figure 3.5. Regions of interest used for individual analyses of spatial separation of peak activity and extent of activation during Spanish and English picture naming. BA44 and BA45 were identified in both hemispheres using the Juelich Histological Atlas (Eickhoff et al., 2005, 2007, 2006).

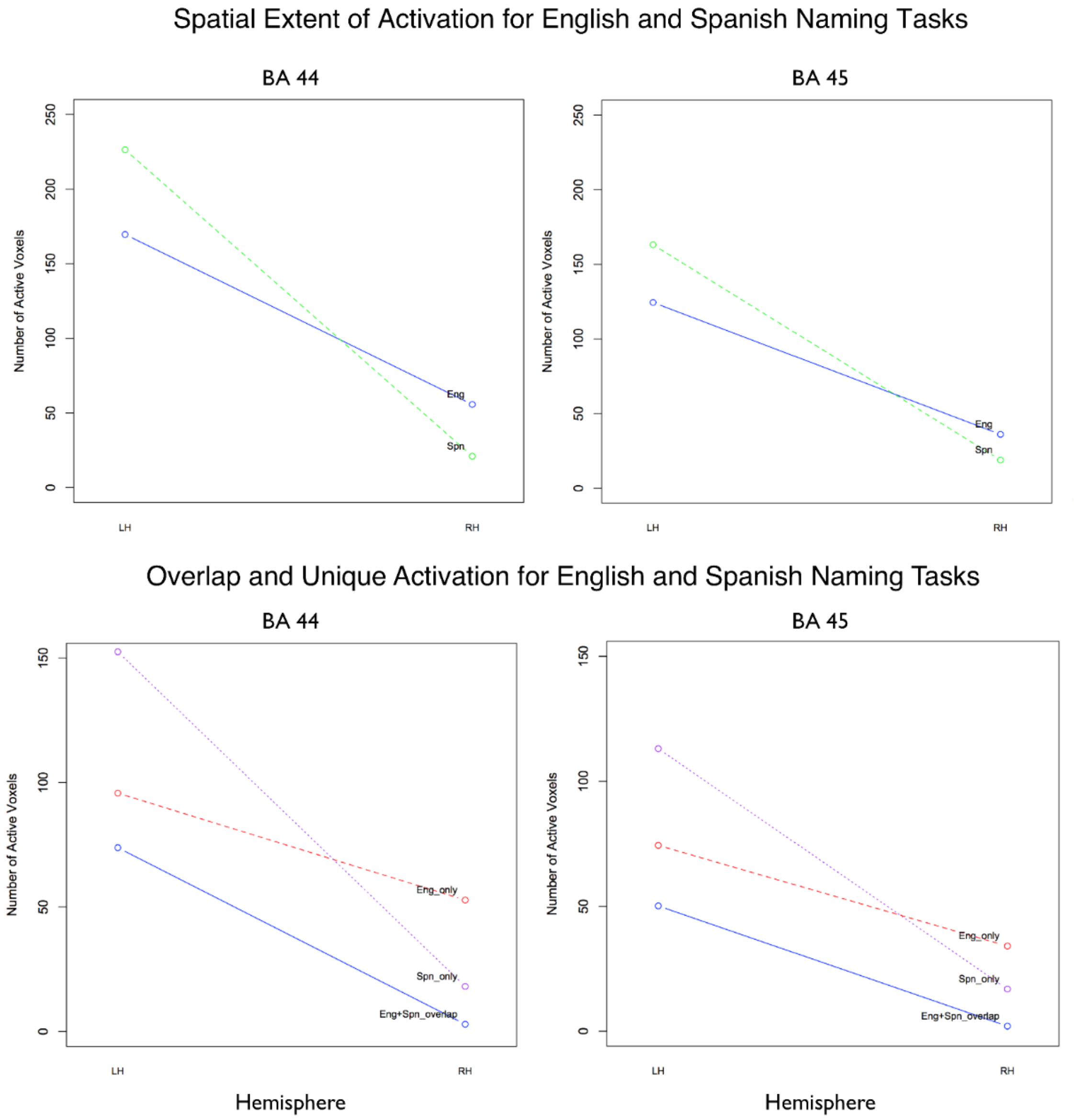

Figure 3.6. Data showing raw number of voxels active in the left and right hemispheres for English and Spanish, and for both languages. a) Graphical representation of the number of voxels that were active during Spanish naming, English naming, or for both conditions in BA44 and BA45 in the LH and RH. b) represents the proportion of voxels that were active during English and Spanish picture naming in BA44 and BA45 of the LH and RH.

3.6 SUMMARY AND LINKING STATEMENT FOR CHAPTER 4

Chapter 3 aimed to identify cortical areas associated with effortful lexical retrieval and articulation of a second language. Although previous research has identified a more extensive network of cortical activity for L2 than L1 processing, which included RH language homologues (Raboyeau et al., 2008), we found evidence of limited language-based activity during the initial stages of L2 acquisition. Thus, although production of newly acquired Spanish vocabulary can be considered effortful lexical retrieval and articulation, it would appear that very low familiarity with the novel language is insufficient to activate the full language network in the brain.

Nevertheless, as we will describe in Chapter 4, we did find some evidence of limited RH activity for Spanish in some participants at the individual level, and high levels of individual and group averaged cortical activity in the RH during lexical retrieval in English. In Chapter 4 we will attempt to further our understanding of the role that RH language homologues play in language production in healthy individuals by using transcranial magnetic stimulation (TMS) to selectively inhibit cortical activation that was present at the individual level for each subject in either the RH or the LH.

CHAPTER 4 WHAT ARE THE EFFECTS OF cTBS OVER BROCA'S AREA AND BROCA'S HOMOLOGUE ON LANGUAGE LEARNING AND PRODUCTION?

4.1 ABSTRACT

In low-proficiency bilinguals speaking their second language (L2), higher levels of activation in right hemisphere (RH) homologues of primary language regions have been observed relative to speech production in their first language (L1). However, the role that the RH plays in L2 acquisition remains unclear. We applied a single session of continuous theta burst stimulation (cTBS) over Broca's area and Broca's homologue in 34 adults who had recently learned vocabulary in a language new to them, to test the effects of inhibitory stimulation on lexical retrieval and articulation. Participants completed picture-naming tests in their native English, and on newly learned Spanish vocabulary. The application of cTBS yielded no consistent effects on speed or accuracy of picture naming. Thus, our results provide no support for the hypothesis that Broca's homologue in the RH is necessary for lexical retrieval and articulation in an L2.

4.2 INTRODUCTION

4.2.1 LANGUAGE ORGANIZATION IN THE BRAIN

Although the majority of our understanding of language functioning in the brain has been derived from research on individuals with brain lesions, more recently researchers have used a technique know as transcranial magnetic stimulation (TMS) to transiently induce virtual lesions in healthy individuals to further understand language circuitry in the brain. One area that has been consistently implicated in speech production is Broca's area in the left inferior frontal gyrus (IFG). Both the pars opercularis (BA44) and pars triangularis (BA45) of Broca's area have been implicated in phonological and semantic processing tasks, albeit with mixed results regarding specialization for these two components of language processing. A meta analysis of studies investigating language tasks indicated that the pars opercularis is more specialized for semantic than phonological processing, along with the ventral pars triangularis and pars orbitalis, whereas the dorsal pars triangularis is more specialized for phonological processing (Vigneau et al., 2006). In spite of this, individual studies have yielded contrasting evidence, that suggests a role for the superior pars opercularis in phonological processing and motor speech generation (e.g. Heim & Friederici, 2003; See Price, 2000; Zatorre, Meyer, Gjedde, & Evans, 1996 for reviews), and for the pars triangularis in semantic processing (Schnur et al., 2009). However, given the high degree of variability reported in the literature for activity during phonological and semantic tasks (See Figure 1 in Vigneau et al., 2006), and the low spatial resolution (7mm limit) for data clustering in the meta analysis, it is difficult to say with certainty that functional specialization occurs at the regional level as suggested by Vigneau et al. (2006), as opposed to an intermingling of component specific groups of neurons within Broca's area.

Although it is commonly understood that the left hemisphere (LH) of the brain is the dominant hemisphere for language, research findings have shown some variability with respect to language lateralization and brain activity during language tasks. For example Knecht and colleagues have reported that bilateral language activation is a natural phenomenon that correlates with handedness in the general population (Knecht et al., 2003; Knecht, Deppe, et al., 2000; Knecht, Dräger, et al., 2000). However, a meta analysis investigating phonological, semantic, and syntactical processing in the RH revealed a lack of specificity of any region for any single component of language (Vigneau et al., 2011), rather, RH language homologues were implicated in the integration of complex verbal material in working memory during language tasks.

4.2.2 CORTICAL ACTIVATION ASSOCIATED WITH SECOND LANGUAGE PRODUCTION

In contrast to the findings reviewed above for native language processing, a number of studies have suggested a greater role for the right hemisphere (RH) in second language (L2) acquisition and use (Golestani et al., 2006; Liu et al., 2010; H. R. P. Park et al., 2012; Raboyeau et al., 2004, 2008). For example, Raboyeau et al. (Raboyeau et al., 2004, 2008) reported activity in right insular and inferior frontal regions in healthy individuals during retrieval of previously acquired, but forgotten words in an L2 (Raboyeau et al., 2008). Likewise, more widely distributed language networks have been reported in late bilinguals, who have been found to exhibit more right frontal and insula involvement than monolinguals (H. R. P. Park et al., 2012), and more bilateral frontal activity when generating words in their L2 compared to L1 (Perani et al., 2003). Based on the common observation that language production is typically more effortful in an L2 than an L1 (Green, 1986;

Perani et al., 2003; Raboyeau et al., 2008; Rudner & Rönnberg, 2008), RH activity has been hypothesized to reflect effortful lexical retrieval and articulation during L2 production (Raboyeau et al., 2008). Accessing and producing words in a language that one is less proficient in may require additional attentional and working memory resources for the integration of complex verbal information (Perani et al., 2003; Raboyeau et al., 2010; Rudner & Rönnberg, 2008).

Raboyeau et al. (2008) have noted that increased RH activity is similarly observed in people with aphasia following LH damage. These authors have suggested that RH language homologues may provide a similar function to that seen in post-stroke aphasia (Raboyeau et al., 2008) during effortful lexical retrieval and articulation of words in an L2. Thus studies of L2 learning may inform both our understanding of L2 acquisition, and of aphasia recovery.

4.2.3 REORGANIZATION AND RECOVERY OF LANGUAGE FOLLOWING LEFT HEMISPHERE STROKE

Damage to primary LH language regions has been found to result in unusually high levels of RH cortical activity during language processing tasks in the subacute stage of aphasia recovery, generating an interhemispheric shift in cortical language representation (Y. Kim, Ko, Parrish, & Kim, 2002; Rosen et al., 2000; Saur et al., 2006; Thulborn et al., 1999). Based on the theory of interhemispheric competition (Fregni & Pascual-Leone, 2007; Mesulam, 1999), which holds that dominant language regions in the LH exert an inhibitory influence over their RH homologues (Netz, 1995, 1999), it is hypothesized that an increase in RH activity following a LH lesion results from reduced transcallosal inhibition, or a release of

RH frontal activity (Price & Crinion, 2005; Thiel, Schumacher, et al., 2006; Thulborn et al., 1999). Alternatively, the functional recruitment hypothesis suggests that undamaged RH regions that are functionally connected to the speech network but not normally needed for language processing, are recruited through an inter-hemispheric shift in language networks in order to compensate for aphasic impairment (Musso et al., 1999; Rosen et al., 2000; Saur et al., 2006). However, whereas normalization of activation, with a shift of activity back to LH regions, has been observed in recovered patients (Karbe, Thiel, et al., 1998; Saur et al., 2006), with more efficient restoration of language occurring when left perilesional areas are preserved or recruited (Fernandez et al., 2004; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Thiel, Habedank, et al., 2006), chronic RH activity is thought to be maladaptive and an impediment to optimal recovery (Belin et al., 1996; Karbe, Thiel, et al., 1998; Martin et al., 2004; Naeser et al., 2004; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al., 2005). For example, based on longitudinal neuroimaging data of individuals with aphasia, Saur et al. (2006) have suggested that over time, recovery of language function is associated with a decrease in RH activity and a concomitant increase in perilesional LH activity.

Over the past decade, a number of studies have reported improvements in expressive language functioning in small groups of patients with chronic (Barwood et al., 2011; Kakuda, Abo, Kaito, et al., 2010; Kakuda, Abo, Uruma, et al., 2010; Malcolm et al., 2007; Martin et al., 2004, 2009; Naeser et al., 2010; Naeser, Martin, Nicholas, Baker, Seekins, Helm-Estabrooks, et al., 2005; Tsai et al., 2014) or subacute (Hamilton et al., 2010; Khedr et al., 2014; Kindler et al., 2012; Thiel et al., 2013;

Weiduschat et al., 2011) aphasia, following a series of treatments with inhibitory repetitive transcranial magnetic stimulation (rTMS) over the right IFG (see Shah, Szaflarski, Allendorfer, & Hamilton, 2013 for a review). The application of inhibitory rTMS to RH language homologues is believed to serve as a form of constraint therapy (Rosen et al., 2000; Taub, 1977), which restricts use of the undamaged function (i.e. compensatory activity in RH language homologues) in order to force use of the affected (LH) function.

Recently, Thiel et al. (2013) reported a significant improvement in language functioning in aphasic individuals who were treated with 10 sessions of inhibitory rTMS over the right pars triangluaris followed by speech language therapy (SLT) compared to sham TMS with SLT. Consistent with previous research that has demonstrated a linear relationship between language recovery and recuperation of LH language regions (e.g. Karbe et al., 1998; Naeser et al., 2004; Thiel, Habedank, et al., 2006), improvement in the treatment group was accompanied by a leftward shift in cortical functioning, with greater recovery of LH function associated with greater improvements in language performance (Thiel et al., 2013). The authors interpreted the results as evidence that reactivating the dominant LH language network through inhibition of activity in RH language homologues can facilitate recovery of language function in aphasic patients.

Raboyeau et al. (2008) have suggested that functional recruitment of RH language homologues may occur both during effortful language production in aphasia and during effortful lexical retrieval and articulation of an L2. Given the apparent facilitatory effect of inhibiting RH activity in individuals with aphasia, inhibition of RH homologues may similarly result in improved language acquisition in L2 learners.

4.2.4 TMS AND LANGUGE FUNCTIONING IN NON-APHASICS

The inhibitory effects of TMS have been described as creating a 'virtual cortical lesion', which can be used to study the contribution of a specific cortical region to a particular behavioural function (Pascual-Leone et al., 2000). Based on the hypothesis that inhibitory rTMS provides a model of focal cortical lesions, and that rTMS delivered to cortical language regions may therefore mimic the effects of an aphasic stroke (Andoh & Martinot, 2008; Knecht et al., 2002), inhibitory TMS has been applied to language areas in healthy controls.

Early TMS studies that used an 'online' stimulation protocol, in which behavioural effects are evident during stimulation, but disappear once the stimulus is removed, reported that speech disruption or arrest occurred during brief (1-10 second) sessions of rTMS at varying frequency (from 8 Hz to over 30 Hz) over LH regions corresponding to Broca's area (Jennum et al., 1994; Pascual-Leone et al., 1991; Wassermann et al., 1999). More recent studies that used online stimulation protocols over different parts of Broca's area have reported interference with different aspects of language functioning. For example, brief (300ms) trains of 10-Hz rTMS applied to the left anterior IFG (BA45/47) 100ms after presentation of a visual stimulus interfered with speed on a semantic decision task (Devlin et al., 2003); and brief high frequency trains of rTMS applied to the left pars opercularis impaired accuracy during a phonological working memory task (Nixon et al., 2004). In a combined TMS and positron emission tomography (PET) study, Thiel, Schumacher, et al. (2006) demonstrated that inhibitory (4 Hz) rTMS to the pars triangularis resulted in increased reaction time latencies along with decreased activity in the left, but increased activity in the right IFG during a verb generation task, compared to verb generation in the absence of TMS.

Other studies have used “offline” stimulation protocols, which have been found to induce lasting inhibitory effects that endure beyond removal of the stimulus. These protocols include low frequency rTMS (which uses magnetic pulses repeated at a rate of 1Hz for approximately 20 minutes; e.g., Naeser, Martin, Nicholas, Baker, Seekins, Helm-Estabrooks, et al., 2005), and cTBS (using bursts of three, 50 Hz pulses delivered at intervals of 200ms typically for 40 seconds; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Such offline studies have reported mixed results in terms of effects on language processing. Knecht et al. (2002) examined changes in reaction time and accuracy on a picture-word verification task following 10 minutes of inhibitory rTMS delivered at 1Hz over Wernicke’s area or its RH homologue. They found that rTMS to the hemisphere identified as dominant for language in each individual increased reaction time in this task. They further reported that participants with strong left or right language lateralization had strong interference effects of TMS over the language dominant hemisphere, whereas participants with more bilateral lateralization showed only minor effects of TMS (Knecht et al., 2002).

In contrast, Andoh et al. (2006) reported that low frequency rTMS applied to Wernicke's area facilitated reaction time on a language-fragment detection task in both native and foreign languages. Andoh et al. further reported that stimulation of the pars opercularis resulted in neither facilitation nor disruption of performance on this receptive language task. Similarly, Restle et al. (2012) found that inhibitory cTBS over the left posterior IFG, with stimulation sites in either the posterior portion of the pars opercularis or the precentral gyrus, had no effect on repetition accuracy for foreign phrases, although excitatory, intermittent TBS (iTBS) improved repetition accuracy compared to sham stimulation.

In contrast to the present study, both Andoh et al. (2006) and Restle et al. (2012) used MRI guided target localization based on group-level functional activation derived from receptive, rather than expressive language tasks. To date, we are aware of no study that has examined the effect of functionally guided inhibitory rTMS on lexical retrieval and articulation that has used individual fMRI data that reflects cortical activity during expressive language tasks to guide target selection. Thus, despite previous studies that have reported no significant disruptive effect of inhibitory rTMS to Broca's area on language processing (Andoh et al., 2006; Restle et al., 2012) following group level fMRI guided TMS, a protocol in which individual cortical activity is used to generate targets for stimulation may yield significant results.

Furthermore, at the time this study was conducted we were aware of no published studies that had examined the effects of inhibitory rTMS over RH language homologues in healthy individuals. As reviewed above, inhibition of RH language homologues that show overactivity in individuals with aphasia, combined with SLT, has led to improved language functioning and a subsequent increase in LH activation (Thiel et al., 2013). Given the proposed similarities between low proficiency L2 learners and aphasics, on the basis of similar patterns of RH activity in these two populations (Raboyeau et al., 2008), it is possible that inhibitory stimulation over the non-dominant hemisphere for language may have the potential to enhance verbal learning (Floel et al., 2008). However, we are aware of no study that has examined the effects of inhibitory rTMS over the RH on the early stages of L2 learning.

4.2.5 THE PRESENT STUDY

The present study was designed to answer two questions. Firstly, can lexical retrieval and articulation in either L1 or a newly acquired L2 be modulated through the application of inhibitory cTBS to regions with activation specific to lexical retrieval and articulation in L1 or L2? Secondly, given findings that the application of inhibitory rTMS may enhance the effects of speech language therapy following stroke (Thiel et al., 2013), does inhibitory cTBS over functionally active regions of Broca's homologue in the RH have a facilitatory effect on learning new L2 words taught immediately after cTBS? To answer these questions we used neuronavigation based on individual functional activation maps to target and stimulate regions within Broca's area and its RH homologue that showed functional activity during a picture-naming task that involved lexical retrieval and articulation. Our participants were unilingual individuals who were taught L2 words for the first time.

We hypothesized that cTBS over Broca's area would modify task performance by decreasing naming performance in English, since this region has been found to be involved in speech production (Nixon et al., 2004; Price, 2000; Zatorre et al., 1996). We further hypothesized that cTBS over Broca's homologue in the RH would interfere selectively with L2 performance, as it has been suggested that this area is involved in effortful lexical retrieval and articulation associated with L2 acquisition (Raboyeau et al., 2008). As well, based on findings that stimulation may be modulated by laterality of language functioning (Knecht et al., 2002), we hypothesized that response to cTBS may be strongest in those for whom cTBS is delivered over the hemisphere that is dominant for language. However, based on findings that individuals with aphasia ultimately demonstrated long-term gains in language abilities following inhibitory rTMS over RH frontal regions (Barwood et al., 2011; Kakuda, Abo, Kaito, et al., 2010; Kakuda, Abo, Uruma, et al., 2010; Khedr et al., 2014; Malcolm et al., 2007; Martin et al., 2004, 2009; Naeser et al., 2010; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al., 2005; Thiel et al., 2013; Tsai et al., 2014), we also hypothesized that individuals who received cTBS over the RH would demonstrate an increased capacity for L2 learning following cTBS as compared to those who received LH stimulation.

4.3 MATERIALS AND METHODS

4.3.1 PARTICIPANTS

Thirty-four healthy right-handed participants (12 women, mean age 43.7, SD 10.6) with no known history of neurological or physiological disease and who were free from any contraindications to MRI or TMS were included in this study. All participants had participated in previous studies that involved second language acquisition and fMRI investigation of activity during L1 and L2 lexical retrieval. Participants had an average of 17 years of formal education (SD = 2.7), and all performed in the average to superior range on a number of working memory and processing speed tests including Trail Making Test A and B, Digit Symbol Coding from the WAIS-III, and Letter-Number Sequencing and Spatial Span from the WMS-III. Participants were unilingual native English speakers with no previous training in Spanish. Both male and female participants were randomly assigned to receive cTBS to either Broca's area in the LH or Broca's homologue in the RH such that each group had an equal number of men and women. The details of specific target selection for cTBS in each participant are described below. Demographic variables for both groups are presented in Table 4.1.

This study was approved by both the Capital Health and IWK Research Ethics Boards in Halifax, Nova Scotia and followed the safety guidelines for TMS outlined by Chen et al. (1997) and Wassermann et al. (1996). Each subject gave written informed consent after receiving a description of the study and an explanation of the potential consequences associated with participation.

4.3.2 GENERAL STUDY PROCEDURE

The following provides a high-level general study overview. Each component of the study is described in more detail in subsequent sections.

All participants completed a three-day study (See Table 4.2) that took place over a three (n = 29) or four (n = 5) day period and involved computerized L2 training, functional magnetic resonance imaging (fMRI), and cTBS. On the first day participants completed the first LANGA session, which involved intensive second language training of 24 words. On the second day, the second LANGA training session, including a review of words they had learned during the first session, was completed immediately prior to an fMRI scan. On the third day participants completed the TMS portion of the study. Participants began the TMS portion of the study by completing a test of picture naming in Spanish and in English (Time 1) to determine their proficiency after the first two LANGA sessions. Prior to the cTBS session, each participant was randomly assigned to receive cTBS to a previously identified target region in either the right or left hemisphere. TMS output intensity was determined for each participant based on his or her individual resting motor threshold (described below). Following cTBS, all participants were instructed to rest for 10 minutes, after which participants were given a second, post-TMS picture naming test of Spanish and English (Time 2). Participants then played a third session of LANGA to determine the effect of cTBS on language learning. Finally, participants completed a third test of English and Spanish naming (Time 3).

4.3.3 OUTCOME MEASURES

At all three timepoints, English and Spanish naming ability was assessed using a series of three equivalent English and Spanish naming tests that were developed using Presentation software (Version 16.3 Build 12.20.12; http://www.neurobs.com). Spanish naming tests contained the same words as trained during the LANGA sessions, but with different pictures to ensure that testing measured generalized lexical retrieval. Each naming test was composed of 48 pictures, which were presented on a computer screen in six arrays of eight pictures each for a limited period of time (8 seconds for Spanish and 6 seconds for English tests). Participants were instructed to name the pictures from left to right across the top row followed by the bottom row as quickly as possible, and told that they could skip a word if they were unable to name the picture. The pictures used in each array across the three English and Spanish naming tests was held constant, but the order in which the pictures were displayed in each array was randomized for each participant and for each test in order to account for any confounding effects of word order. During naming tests, participants wore a Logitech (Morges, Switzerland) headset with built-in microphone to facilitate high quality recording of verbal responses. Verbal responses were recorded and each word in each array was scored to yield a total naming score.

For all three naming tests, each word that participants said in Spanish was scored on a 5-point Likert type scale using the following criteria: A perfect word and preposition received 4 points; a perfect word with an absent or incorrect preposition, or a word that was almost perfect save for a slight deviation in pronunciation received 3 points; if the word uttered was imperfect, but recognizable as the target word, two points were awarded; a word that was clearly not correct, but that did resemble the target word in some way received 1 point; and words that did not resemble the target word in any way, or no response received a score of 0. Because there was less variability in English naming performance across participants, English words were scored on a 3-point Likert type scale using the following criteria: A perfect word received 2 points, an improperly pronounced or partial word that was recognized as correct received 1 point and an incorrect or no response received 0 points.

The total score for Spanish and English naming tests at all three timepoints was calculated for each participant by a minimum of two out of six possible raters, and average scores across raters were obtained for each participant in each condition. Inter rater reliability was calculated using SPSS for Windows, version 20 (IBM statistics). Cohen's kappa (κ) ranged from κ = .700 to .789. Average naming scores across timepoints are presented in Table 4.3 for each group.

4.3.4 DETERMINATION OF TMS TARGETS FROM MR IMAGES

Each participant took part in an fMRI experiment to determine regions of the brain that were active during English or Spanish naming tasks respectively. MRI scans were acquired using the GE 1.5 Signa Excite scanner located at the IWK Health Centre. The study design consisted of four fMRI runs, two each of English naming and Spanish naming, with a blocked experimental design consisting of five 30-second naming blocks, five 30-second control blocks, and seven 15-second rest blocks each. An example of an fMRI run is presented in Figure 4.1. During Spanish naming blocks participants were shown pictures from the LANGA training program, and during English naming blocks participants were shown 45 pictures chosen from the Rossion-Pourtois Picture set (Rossion & Pourtois, 2004), a standardized set of 260 coloured line drawings. Each naming block consisted of nine pictures randomly presented for 3300ms each, for a total of 45 pictures in each run. During active control blocks participants were instructed to verbalize the word 'picture' in response to scrambled images to control for brain activation during lexical retrieval and articulation of well-learned words, as well as visual stimulation. Rest blocks represented a passive baseline condition that involved simply staring at a fixation cross. MRI data processing was carried out using the FSL software package (Smith et al., 2004; Woolrich et al., 2009) following standard procedures developed in our lab and used in our previous publications (Newman, Bavelier, Corina, Jezzard, & Neville, 2002; Newman, Supalla, Hauser, Newport, & Bavelier, 2010a, 2010b).

Brain areas that were activated by each naming condition relative to active and passive control conditions were identified using a fixed effects model (FLAME; Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004; Woolrich, 2008). Functional activity was identified using a cluster threshold of Z > 2.3 and a corrected cluster significance threshold of $p = .05$.

Identification of Broca's area was made on the basis of each participant's anatomical MRI scan defined by the region that was delimited dorsally by the inferior frontal sulcus, ventrally by the Sylvian fissure, and was located anterior or rostral to the precentral gyrus (Andoh et al., 2006; Devlin et al., 2003; Nixon et al., 2004). Identification of individual cortical folds was obtained from coronal and sagittal MRI slices using FSLview (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) and 3D rendering of the cortex using Brainsight software (www.rogue-research.com). Cortical areas along the inferior frontal gyrus that demonstrated activity during Spanish and English naming blocks relative to active and passive control conditions were identified for each participant. In all cases, BA44 and BA45 within Broca's area were readily apparent from each participant's anatomical MR image.

Consistent with findings reported by Pascuale-Leone (1991), Jennum (1994), and Wassermann (1999), pilot testing showed that 10 Hz rTMS for 10 seconds over BA44, but not over other adjacent areas, disrupted speech production for the duration of stimulation during a counting task. In the present study, this finding was reproduced in three pilot subjects. Thus, for each participant, efforts were made to identify regions to be used as targets for TMS that were active during naming tasks (i.e., identified based on fMRI analysis) and located within BA44 or its homologue. In the event that functional activity was not present within BA44 or its homologue, but was present in adjacent BA45, the cortical activity in BA45 was used as a target for TMS. In the rare event that no activity was present in either BA44 or BA45, TMS was delivered based on anatomical identification of BA44 (as described above).

Although functional activity varied considerably at the individual level, the majority of participants (17/34) had both English and Spanish activity present in the target region selected for cTBS. Nine participants had English activity only in the target region, with three of these evidencing subthreshold or insular Spanish activity as well. Five participants had only Spanish activity in the target region. One participant had only subthreshold English activity and one participant had only subthreshold Spanish activity. In only one case, no activity was present in the target region and the ROI was determined based on the anatomically defined BA44. These results are summarized in Figure 4.2. This experiment and the procedure used to analyze the fMRI data is described in more detail elsewhere (Chevalier et al., manuscript in preparation).

Laterality Index (LI) was calculated for each language and for each participant using the number of active voxels within known language areas (inferior frontal gyrus: opercularis, triangularis, orbitalis, the operculum and insula) in each hemisphere using the formula (LH-RH) / (LH+RH). For both English and Spanish, naming activity relative to active and passive control conditions was included to ensure that we considered only activation that was present during naming tasks. Table 4.4 provides the lateralization indices for English and Spanish naming for all subjects. For English naming, laterality ranged from -1 to 1 (Mean = 0.095, SD = 0.54). For Spanish naming, laterality ranged from -1 to 1 (Mean = 0.476, SD = 0.527). However, Spanish and English laterality scores were not correlated among participants. Laterality index scores differed significantly across our sample [t(26) = -2.134, $p < .05$] as participants overall had greater left laterality for Spanish than for English.

4.3.5 TMS PROCEDURE

In all cases, the TMS session took place either one (N = 31) or two (N = 3) days after the fMRI scan was obtained. To facilitate focal stimulation of the targeted brain regions, neuronavigated TMS was performed using a frameless stereotaxic system (Brainsight; Rogue Research, Montreal, Canada; http://www.rogue-research.com). Brainsight software (Version 2.2.8; Rogue Research Inc., 2013) was used to track and guide the TMS coil position in real-time, facilitating optimal coil positioning for each target site. Briefly, each participant's anatomical MRI scan was imported into Brainsight, which generated a virtual three-dimensional reconstruction of each participant's brain, head and scalp. The functional MRI data for each participant were overlayed on the reconstructed anatomical brain image in order to determine an appropriate target for stimulation. Next, the reconstruction of the head and scalp was co-registered to each subject and the coil using between 4 and 8 anatomical landmarks depending on quality of registration (i.e., tip of the nose, bridge of the nose, preauricular points, and in some cases other clearly identifiable points on the left and right ears including the tragus and the point at which the helix joins the scalp, and the corners of the mouth). This registration allowed for real-time visualization of coil position in relation to functional and structural MRI data. Participants were positioned in a reclined seat with a headrest positioned over the contralateral hemisphere to which TMS was applied to hold their heads relatively immobile during stimulation (See Figure 4.3). The coil was placed tangential to the head at the point of contact and held such that its handle pointed down and backward at an angle approximately 45 degrees to the sagittal plane, with the second phase of the biphasic pulse inducing a posterior-to-anterior current flow (Bolognini & Ro, 2010; Hallett, 2000; Hartwigsen et al., 2013). Constant coil positioning was maintained by monitoring the computerized display during stimulation. TMS was applied using a Magstim Super Rapid^2 Plus[1] (www.magstim.com) with a 70 mm air-cooled figure of eight coil. Motor thresholds ranged from 36 to 68% maximum stimulator output (mean = 53.62, SD = 7.85). The MNI coordinates of the individual cTBS sites are provided in Figure 4.4 and Table 4.4.

The total number of stimuli and duration of the train of stimulation were applied according to the protocol set forth by Huang and colleagues (Huang et al., 2005), which has been used with both clinical and control participants (Huang et al., 2005, 2011; Kindler et al., 2012; Nardone et al., 2011; Restle et al., 2012). cTBS was carried out according to international consensus guidelines (Rossi et al., 2009; Rossi, Hallett, Rossini, & Pascual-Leone, 2011; Wassermann, 1998) for the safe application of TBS.

Prior to stimulation with TBS, the TMS output intensity was determined for each participant according to standard operating procedures used in the laboratory (see Appendix C and D). First, the resting motor threshold (RMT) was determined. RMT is defined as the minimal intensity of the TMS device output at which a motor evoked potential of an amplitude of ≥ 50 μV [detected via surface electromyography (EMG) overlying the muscle of interest] can be seen on 5 out of 10 trials after stimulation of the corresponding cortical area. On each participant's reconstructed

MRI scan, a virtual 5cm x 5cm grid was positioned evenly on the virtual surface of the brain, such that the centre of the grid corresponded to the region of the precentral gyrus that appeared to correspond to the left hand; the grid consisted of 25 targets spaced 1cm apart. Starting with the centre point on the grid, a single TMS pulse was delivered at 30% of the stimulator output, and increased in increments of 5% while monitoring for the occurrence of a motor evoked potential in the pointer finger of the left hand. This procedure was completed for target points on the grid until a motor 'hotspot' – the location that yields the largest MEP amplitude with the lowest stimulator intensity on 5 out of 10 trials – was identified. The stimulus intensity that elicited MEPs of an amplitude of ≥ 50 μV on 5 of 10 trials at the motor hotspot was considered to represent RMT. The stimulus intensity used for the subsequent TBS was set at 90% of the derived RMT (90% RMT) following established practices (Huang et al., 2005, 2011; Kindler et al., 2012; Nardone et al., 2011; Restle et al., 2012). For four participants, 90% RMT exceeded the maximum stimulus capacity for the cTBS protocol, and so stimulus intensity was set to the maximum (57%), which resulted in an average stimulus intensity of 85.25% MEP (SD = 0.96, range = 84-86%) for these four participants. Average MEP and stimulation intensity for both groups is presented in Table 4.1. Using the neuronavigation system as described above, the TMS coil was placed over the region of interest in either the right or left hemisphere for cTBS. cTBS was then delivered in bursts of three stimuli at 50Hz pulses, repeated at intervals of 200ms for a total of 600 pulses. The duration of stimulation ranged from 39 to 47 seconds for each participant, depending on the output intensity used.

4.3.6 STATISTICAL ANALYSIS

Potential pre-TMS differences between participants in the group that received RH stimulation and the group that received LH stimulation were analyzed using a multiple analysis of variance (MANOVA); differences in naming performance from pre- to post-TMS (see Outcome Measures, Section 4.3.3) for each group were conducted via paired samples t-tests using SPSS for Windows, version 20 (IBM statistics). Linear mixed effects were calculated using The R Project for Statistical Computing (Version 3.1.0; http://www.r-project.org/). Grouping variable was side of stimulation, and repeated measures included English and Spanish naming across all three timepoints. A linear mixed effects model was performed for both English and Spanish naming to investigate the effects of cTBS site (right or left Broca's area) on change in naming score over time, while accounting for any potential contribution of age or language laterality to the effects of cTBS. Average naming scores achieved during the third, post-TMS LANGA session were compared to those achieved during the first and second sessions of LANGA to analyze the effect of cTBS on L2 learning (see Table 4.3). To explore any other effects that subjects may have perceived following cTBS, such as changes in mood or perceived performance, subjects were asked to describe any subjective changes in mood or functioning following the session. Subjects were also asked to describe their sense of discomfort/pain following the TMS session.

4.4 RESULTS

All participants reported discomfort caused by cTBS over Broca's area due to uncontrollable contraction of the facial muscles, such that disposable sports mouth guards were made available to participants 12 through 34 to offset the effects of jaw clenching and reduce the potential for injury. Additionally four participants reported experiencing low-grade headache for up to a week following the TMS session. Otherwise, the procedure was well tolerated with no lasting adverse effects in any participant, and none of the participants asked to withdraw their participation.

MANOVA revealed no statistically significant pre-treatment differences between groups on Age, Education, MEP, Laterality Indices, Spanish or English Naming score, nor on any of the working memory or processing speed measures. Descriptive statistics for both groups are presented in Table 4.1.

4.4.1 EFFECTS OF TMS ON TARGETED LANGUAGE AREAS

Across the full sample, no significant differences were identified between pre- and post-cTBS English naming (t = 0.207, p = .838) or pre- and post- Spanish naming (t = 0.451, p = .655). At the group level, pairwise t-tests comparing pre- to post- cTBS naming scores in Spanish and in English revealed no statistically significant pre- to post- cTBS changes for either the group that received right hemisphere stimulation (English: t = 0.441, p = .665; Spanish: t = 0.567, p = .578) or for the group that received left hemisphere stimulation (English: t = -0.087, p = .932;

Spanish: $t = -0.070$, $p = .945$). Means and standard deviations of all naming scores for both groups are presented in Table 4.3.

In light of the non-significant results reported above, we conducted a linear mixed effects analysis to ascertain whether changes occurred due to cTBS across the three timepoints (pre-cTBS, post-cTBS, post LANGA training) for either English or Spanish naming, and to explore the possibility that any change in naming score may have been influenced by either laterality index or age. For English naming, side of stimulation did not explain a significant amount of variance from a modeling perspective, and as such, it was not included in the best model. Time, age, and laterality index were retained in the model. There were no statistically significant main effects of age ($p = 0.41$), laterality index ($p = 0.47$), or time ($p = 0.90$) on English naming score. A significant interaction emerged between time and age $F(2, 56) = 4.24$, $p < .05$. Although the slope of the age effect was not significantly different from zero at any time point, a plot of the interaction effect (Figure 4.5) revealed that the slope of the line for English naming performance and age varied as a function of time, indicating a potential relationship between age and response to cTBS. To further explore this observation, we created a new variable, *percent change*, by subtracting each participant's post-TBS score from the pre-TBS score, and dividing the result by the pre-TBS score. We found a significant correlation ($r = .479$, $p = .004$) between age and percent change in English naming, indicating that regardless of stimulation side, older participants were more adversely affected than younger participants by cTBS. The interaction between time and laterality index was also statistically significant $F(2, 56) = 5.29$, $p < .01$. However, as there was no meaningful relationship between laterality index and time when side of stimulation was not included in the model, this interaction was not interpreted.

For Spanish naming, side of stimulation, age, and Spanish laterality[2] were retained in the model. There was no significant main effect of stimulation side (p = 0.73) or laterality index (p = 0.36), however there was a significant main effect of age $F(1, 59) = 32.15$, $p < .001$, indicating that across timepoints, younger participants were able to name more Spanish words than older participants. The interaction between age and stimulation side was marginally significant $F(1, 59) =$ 3.89, $p = .053$, indicating that the effect of age on naming was more pronounced for the group that received RH stimulation, independent of time of testing (i.e. pre- or post-TMS).

4.4.2 EFFECT OF cTBS ON LANGUAGE LEARNING

To answer our second question of whether cTBS had any effect on new L2 vocabulary learning, we conducted a linear mixed effects analysis that compared the average word confidence scores (expressed as a percentage) generated by the speech recognition software embedded in the LANGA program for both stimulation groups across the three LANGA training sessions. Results revealed no main effect of stimulation side (p = .59), or of training session (p = .26), indicating that there was no significant difference in average confidence score across the three training

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[2] Spanish laterality was slightly negatively skewed (Skewness = -.85, SE = .43), across the full sample reflecting a tendency towards left hemisphere lateralization for Spanish naming activity, but bimodally distributed in the group that received LH stimulation (Shapiro Wilk (15) = .865, p = .029), thus no transformation was applied.

sessions across the full sample, or between those who received RH or LH stimulation. However, the interaction between stimulation side and training session was significant $F(1, 40229) = 52.76$, $p < .001$. Posthoc t-tests revealed that for the RH stimulation group, average naming scores during LANGA session 3 (mean = 50.31, SD = 10.94) were significantly higher than naming scores during LANGA session 1 (mean = 46.45, SD = 11.64); $t(40229) = -2.33$, $p = .02$. The average scores for each training day for each group are presented in Table 4.3 and in Figure 4.6.

4.4.3 QUALITATIVE OBSERVATIONS

Following the final naming test, participants provided qualitative responses to questions about their performance, mood, and general changes that they may have perceived from pre- to post- TMS. Perceived changes in performance, with respect to speed or accuracy are reported in Table 4.4. When asked, "How do you feel?" the majority of participants (24/34) responded with either 'fine, or good'. When asked generally about any changes perceived from before to after TMS, the majority of participants (19/34) indicated that they had not perceived any specific change.

Responses from those who reported noticing a change unrelated to Spanish or English naming performance following RH TMS are as follows: "My brain feels more tired. My head is dull. I'm out of it a little. I can feel my temples, it's not painful, but it feels like it's about to start a headache" (TMS_05); "I feel like the ground is farther away, like I'm very tall" (TMS_07); " I feel floaty, like there is an aura, kind of surreal. It's a cool feeling" (TMS_08); "I am more relaxed. I am thinking about things more rather than just blurting things out" (TMS_15). Responses from those who received LH stimulation included: "I feel fine. A little queasy, dizzy, kind of 'post fair ride'" (TMS_12); "A little muscle tension but not a concern" (TMS_17); "External discomfort on the muscle of the temple" (TMS_27); "Not good. It kind of put me in a tired mood. I feel tired and a bit spacey" (TMS_29); "Just more fatigued" (TMS_30).

Interestingly, when asked whether participants found that learning new words was easier, harder, or about the same as the previous LANGA session, five participants who received RH TMS reported finding it more difficult to hold the new words that they had learned in memory, despite reporting no difficulties pronouncing the new words. Likewise, eight participants from the LH TMS group reported having difficulties with retention after having learned the words, and four of these reported difficulty with pronunciation of the new words. In contrast, three participants in the LH TMS group found the new words easier to pronounce.

In terms of self-reported changes in mood and/or energy levels following TMS, besides three participants in each group who reported general fatigue, no consistent pattern emerged. In the RH TMS group, one participant reported noticing an increase in energy, another an improved ability to focus, and one reported feeling more relaxed and mellow. In the LH TMS group one participant reported feeling more alert, whereas another participant who also noticed a substantial change in language ability reported low mood following cTBS, but no lasting changes or difficulties were reported upon follow up.

4.5 DISCUSSION

In the present study, we sought to understand the behavioural effects of functionally guided inhibitory cTBS by determining whether a single session of cTBS over either Broca's area or its RH homologue had any effects on either lexical retrieval and articulation in a native or recently acquired language, or on further language acquisition; and whether any differences observed were dependant on stimulation to a specific hemisphere. More specifically, we addressed the question of whether a focal virtual lesion in a region of primary language activation in either the LH or RH would interfere with lexical retrieval and articulation of either English or Spanish words respectively, and whether a focal virtual lesion in Broca's homologue in the RH would facilitate further L2 vocabulary learning.

4.5.1 TMS AND VERBAL OUTPUT IN L1 AND L2

We found no main effects of cTBS on naming ability in either English or Spanish, either across hemispheres or within specified targets, and no causal relationship between cTBS and change in picture naming scores for either language. Although a small number of participants evidenced either an improvement or a decline in naming performance following cTBS, there was no consistent effect of stimulation on language production across participants, and no factor was able to account for any observed changes in a meaningful way.

Although several studies have previously demonstrated efficacy of rTMS to Broca's homologue for modulation of language function in chronic (Barwood et al., 2011; Naeser et al., 2010) and subacute (Thiel et al., 2013) stroke patients, findings from TMS studies in healthy controls have been less consistent. Despite findings that excitatory TMS (Devlin et al., 2003; Nixon et al., 2004; Restle et al., 2012) may have a facilitatory effect on language processing, the absence of any effect of TMS over Broca's area has also been reported previously (Andoh et al., 2006; Epstein, 1998; Mottaghy et al., 1999; Sparing et al., 2001). Likewise, Restle et al. (2012) reported that whereas excitatory iTBS over the left posterior IFG improved accuracy during a foreign speech repetition task, no change in performance occurred following inhibitory cTBS, using a protocol similar to that used in the present study. This latter finding indicated that cTBS was not effective in inhibiting the target brain region.

In spite of the overall lack of effects of cTBS on naming, we did find a significant correlation between age and change in English picture naming score following cTBS, regardless of the stimulation target. This relationship between age and stimulation indicates that older adults may be more adversely affected than younger adults by cTBS, irrespective of which side is stimulated.

4.5.2 TMS AND LANGUAGE LEARNING

Based on findings that inhibitory rTMS over the right IFG resulted in improved language abilities in individuals with aphasia (e.g. Barwood et al., 2011; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al., 2005; Thiel et al., 2013), we hypothesized that inhibitory cTBS over Broca's homologue would facilitate foreign vocabulary acquisition. Our results indicated a significant improvement in performance during LANGA training in session 3 as compared to session 1, however there was no significant increase from session 2 to session 3. This suggests that the increase may have been due to practice effects of using LANGA, rather than directly attributable to the application of cTBS. On the other hand, if this is the case it is unclear why these practice effects occurred in one group and not the other.

Following cTBS, a number of participants from both groups reported that they thought it was easier to say new words as they were learning them, but that they had more difficulty remembering the words, or holding the images in mind for use during the learning tasks than they had prior to cTBS. This was interpreted as a perception of having done more poorly on new word learning following cTBS for both groups. Similarly, Knecht et al. (2002) reported that following low frequency (1Hz) TMS, four participants who had improved reaction times on a picture-word verification task reported feeling that they had done more poorly following TMS. This highlights that perceived changes in functioning after TMS may not be accompanied by measureable changes.

4.5.3 NO CORRELATION BETWEEN THE EFFECTS OF TMS AND LANGUAGE LATERALITY

Although Knecht et al. (2002) reported a disruption of receptive language following inhibitory rTMS over Wernicke's area that correlated with language laterality, we were not able to demonstrate a similar effect on expressive language following TMS over Broca's area or Broca's homologue. In the present study we found no relationship between degree of language lateralization and susceptibility to unilateral virtual brain lesion. However, low levels of activation in primary language regions of one or both hemispheres in some participants prevented calculation of laterality index (8 of our 34 participants). Additionally, the between-groups design and the variability in stimulation site across participants prevents us from drawing firm conclusions regarding the relationship between laterality index and the effects of TMS across our sample. Laterality scores and change in naming performance for all participants are presented in Table 4.4.

4.5.4 RECIPROCAL FACILITATION MAY COMPENSATE FOR VIRTUAL LESIONS IN HEALTHY INDIVIDUALS

There are a number of plausible explanations for the finding that inhibition of either Broca's area or its RH homologue did not interfere with lexical retrieval and articulation in either English or Spanish in the present study. For example, the majority of our participants demonstrated a high degree of bilateral cortical organization during language production. Although there was no correlation between laterality and change in naming score, Knecht et al. (2002) likewise reported almost no slowing of verbal processing following inhibitory rTMS in individuals with no marked hemispheric lateralization. Based on these findings they suggested that distributed functioning across both hemispheres may have a protective effect against both virtual and actual lesions (Knecht et al., 2002). Thus, it is possible that a high level of activity in interconnected brain regions may have compensated to some degree for the virtual lesion induced through TMS in our participants.

Hartwigsen et al. (2013) recently reported that cTBS over the left posterior IFG resulted in decreased fMRI activation during word and pseudoword repetition tasks in the left IFG, and increased activity in homologous RH regions. They used dynamic causal modeling of MRI data to investigate the hypothesis that up-regulation of RH regions reflected a release from transcallosal inhibition, however their results indicated that cTBS of the left IFG increased facilitatory drive from the right to the left posterior IFG, but did not change the influence of the left IFG on the right IFG. Correspondingly, there were no statistically significant behavioural effects on naming performance following cTBS. Hartwigsen et al. suggested that these results indicate adaptive reorganization following a virtual lesion in which interconnected regions including the right IFG compensate for the inhibitory effects of cTBS.

Thus, adaptive up-regulation in healthy controls, particularly with bilateral language circuitry involvement may preclude effects of cTBS to primary language areas. These findings are consistent with those that have been reported following connectivity analysis of the effects of rTMS over the motor cortex, in which different stimulation frequencies resulted in rapid reorganization of the motor system, which differed according to stimulation frequency, to compensate for changes in cortical excitability (Rounis et al., 2005).

4.5.5 DOES INHIBITORY cTBS PROVIDE A USEFUL MODEL OF POST-STROKE APHASIA?

Overall, the capacity of intact brain to compensate for the effects of a small, virtually induced cortical lesion suggests the effects of offline inhibitory rTMS may not be sufficient to truly mimic the damage resulting from an aphasic stroke. Previous studies have demonstrated that online rTMS applied to Broca's area may interfere with speech (e.g. Nixon et al., 2004), and offline inhibitory rTMS applied to the motor cortex may result in depressed amplitude of MEPs (e.g. Huang et al., 2005). However, whereas Knecht et al. (2002) reported slowed reaction time on a picture-word verification task after offline rTMS over Wernicke's area that correlated with language laterality, we are aware of no studies that have demonstrated impaired language functioning, similar to that typically seen in the acute or subacute phase after stroke, following offline inhibitory rTMS. Thus, while the results of our study could be explained by the model proposed by Hartweigsen et al., (2013) – that the RH homologue of Broca's area becomes more active and facilitates language processing to support the functions of the inhibited region – the temporary and transient, as well as spatially focal, region of the virtual lesion may provide a limited comparison to an aphasic stroke.

It has been estimated that when applied tangentially to the scalp at perithreshold intensity, TMS affects a cortical volume of approximately 1cc (Roth et al., 1991; Wagner et al., 2004). However, the region of damage following an aphasic stroke is much more extensive than the 1cc virtual lesion induced by TMS. In fact, damage to Broca's area alone is not sufficient to produce Broca's aphasia (Mesulam, 2000), which results from damage to underlying white matter and surrounding cortex in addition to Broca's area. Thus, it is likely that surrounding, undamaged perilesional LH cortex is essential for the effects of RH reciprocal facilitation to effectively support language following stroke, and the facilitatory RH effects may be negated in the event that LH language regions are destroyed completely by stroke (Hartwigsen et al., 2013).

4.5.6 LIMITATIONS

4.5.6.1 Variable Effect of cTBS

Perhaps the most significant limitation of the present study is the variable effect of cTBS that has been reported across individuals. Although cTBS has been reported to have an inhibitory effect on motor function on average, with maximum effects of stimulation occurring approximately 5-10 minutes post stimulation and inhibitory effects that last for approximately 60 minutes (Huang et al., 2005), other studies have not supported these findings. For example, Vallence and colleagues reported a decrease in MEP amplitude immediately following cTBS in 13 out of 18 participants (with decreases ranging from 19 to 76%) and a decrease in 15 of 18 participants 5 minutes post cTBS (with decreases ranging from 4 to 74%). On top of the high variability of the effect, the mean MEP amplitude returned to baseline just 10 minutes post cTBS (Vallence, Kurylowicz, & Ridding, 2013). Similarly, Hamada and colleagues showed that the MEP response to cTBS over the motor cortex is highly variable among individuals, with no significant response to cTBS at the group level, and less than 50% of participants showing the expected response of inhibition after cTBS (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013). In their large (n = 52) sample of healthy controls they found no correlation between response to cTBS and age, gender, or time of day that cTBS was administered. They did find a relationship between TBS response and MEP latency, which was not measured in the present study.

Importantly, studies that investigate the effects of TMS over the motor cortex are able to test the effects of TMS by examining changes in MEP amplitude over time. However, with TMS over language regions, there is no means other than neuroimaging to assess the effects of stimulation. Thus, in the present study, although we cannot rule out that unaffected cortical regions may have compensated for the inhibitory effects induced by TMS, as reported by (Hartwigsen et al., 2013), we also cannot rule out the possibility that cTBS simply did not produce any inhibitory effect in our participants. Additionally, in the present study the post-TMS naming test was administered approximately 10 minutes after cTBS. The choice of this timing was based on Huang et al (2005), which indicated that the inhibitory effect of cTBS begins approximately 5-10 minutes after stimulation. However, given the brief duration of the effects of cTBS demonstrated by Vallence et al. (2013) it is also possible that our outcome measures may have been administered too late to detect an effect.

In fact, given the demonstrated effects of online TMS protocols on both behavioural language functioning (Devlin et al., 2003; Nixon et al., 2004; Thiel, Schumacher, et al., 2006) and cortical activity (Thiel, Schumacher, et al., 2006), a protocol in which participants complete naming tests and subsequent L2 learning during online, inhibitory rTMS may result in more demonstrable effects than the offline protocol used in the present study, and in the studies reviewed above (Hamada et al., 2013; Hartwigsen et al., 2013; Vallence et al., 2013). To date, no comprehensive, comparative studies have been conducted to demonstrate the relative efficacy of the various modalities of noninvasive brain stimulation (NBS; Raffin & Siebner, 2014), or to compare different stimulation paradigms, frequencies, and intensities of stimulation with regards to their respective effects on language function. As well, limited information regarding the functional network effects of NBS illustrates the need for future studies to employ concurrent or post-TMS neuroimaging to investigate brain regions that may mediate the impact of focal TMS on task performance (Sack et al., 2007) and to further understand the causal interplay within the brain (Bestmann et al., 2008).

4.5.6.2 Target Identification and Coil Position

A number of factors may have influenced selection of a target for stimulation and positioning of the TMS coil in the present study. Firstly, several studies have acknowledged the inherent limitation regarding precise coil positioning to ensure maximal effect of TMS. For example, although we were able to monitor coil position to ensure that we were over the specific target we had identified for each participant, we were unable to control for the variable depth of target regions across participants (Andoh et al., 2006; McConnell et al., 2001; Nixon et al., 2004). Thus, participants with primary activation that occurred deeper within the cortex may have had less of an effect of TMS than those who showed more peripheral primary activation, and thereby closer to the point of stimulation.

Secondly, in the present study older participants had much looser skin around the head and face than younger participants, thus limiting the goodness of fit of registration. Although in cases where registration proved difficult up to eight anatomical landmarks were used to guide registration, sometimes the registration did not align perfectly with the MRI data despite these extra efforts (i.e. for some participants the registration appeared to be off by a few millimeters even after several registration attempts). This is likely complicated by the fact that participants lay prone and wore a set of earphones during the MRI, which may have resulted in mild shifting of the skin around the face, relative to the inclined position that participants were placed in for TMS.

Thirdly, across our participants there was variability in strength of activation during naming tasks in cortical regions, with only subthreshold activation present in some participants. In some cases, this made selection of a functionally-based target region challenging.

4.5.6.3 Limitations of Outcome Measures

The naming tests that we used in the present study allowed us to get a sense of participants' ability to name pictures in both English and Spanish within a limited period of time. Although this provided us with a crude measure of both speed and accuracy, we were not able to disentangle the specific effects of TMS on either construct individually. Previous studies have reported increases in naming or processing speed, but no change in accuracy following TMS protocols (i.e. Andoh et al., 2006; Devlin et al., 2003; Mottaghy et al., 1999). Conversely, Wassermann et al. (1999) reported an increase in naming errors, but a paradoxical decrease in reaction time, resulting in faster but less accurate naming following TMS. In the case of the present study, we could not determine whether TMS resulted in a change in only speed or in accuracy as these measures were combined.

Furthermore, based on average naming scores obtained on English and Spanish naming tasks, it was evident that while our English naming task was very easy for participants to complete[3], resulting in a potential ceiling effect, our Spanish task was very difficult for participants to complete, which may have inadvertently created a floor effect. This imbalance in task difficulty may have prevented the detection of a possible improvement in English or a decline in Spanish naming scores. Also, although inter-rater reliability was quite good, ranging from .700 to .789, our rating system allowed for limited differentiation among scores, and words were scored by raters who were not familiar with the Spanish language, which may have affected variability of scores across naming tests.

4.5.6.4 Choice of Control Condition

In the present study, LH and RH stimulation sites were used as controls by which to compare the relative effects of TMS to language regions in one hemisphere against the effects of TMS to language regions in the other. This design falls within the suggestion by Flöel et al. (2008), who recommended that RH control sites be included in studies in which NBS is applied to LH sites. However, we did not include a sham condition, as true sham TMS requires a separate sham coil and is not accompanied by the same degree of discomfort as TMS to the frontal regions, and thereby has the potential to influence expectancy effects. We expected that stimulation of either hemisphere would result in different effects, if a true effect of stimulation were present. For example, we hypothesized that inhibition of RH and LH language regions would result in differential impairment of Spanish and English. We also made an effort to control for potential expectancy effects that may have

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[3] Across the full sample English naming had a platykurtic and negatively skewed distribution (Kurtosis = 2.84, SE = .47; Skewness = -1.31, SE = .403) indicative of a ceiling effect on English naming.

arisen from the lack of a sham condition by not informing participants of our hypotheses regarding side of stimulation or expected impact on language functioning.

4.5.6.5 Missing Data

Finally, due to frequent and varied technical difficulties, we were unable to record the confidence scores for 5 participants as they played the third session of LANGA. This significant loss of data reduced our power to detect any effects of TMS on L2 acquisition.

4.5.6.6 Publication Bias

Although the published evidence appears to be consistent in its support for the use of inhibitory TMS over RH language homologues to support recovery from aphasia (Baker, Rorden, & Fridriksson, 2010; Barwood et al., 2011; Hamilton et al., 2010; Kindler et al., 2012; Thiel et al., 2013; Weiduschat et al., 2011), not all studies have supported this finding (Seniów et al., 2013). It is possible that this may reflect the publication bias that is prevalent in cognitive science, in which studies with non-statistically significant findings are less likely to be published than statistically significant findings (Ioannidis, Munafò, Fusar-Poli, Nosek, & David, 2014). Thus, the possibility that other studies that have found no effects of TMS, but that have not been published, may limit our objective understanding of the usefulness of TMS from the literature.

4.5.7 CONCLUSIONS

Despite previous findings that online inhibitory rTMS may create a focal virtual lesion, which disrupts cortical activity and results in behavioural effects such as speech disruption, we found no effects of offline inhibitory cTBS to either Broca's area or its RH homologue at the group level on lexical retrieval and articulation during English or Spanish naming tests. However, our results indicate that the effects of inhibitory cTBS may vary with age, with older individuals being more adversely affected by cTBS than younger adults in terms of lexical retrieval and articulation of L1 irrespective of stimulation side. Furthermore, our findings provide preliminary evidence that inhibitory cTBS over Broca's RH homologue may facilitate the acquisition of foreign vocabulary, as a small improvement was noted during the third LANGA training session as compared to the first LANGA training session for the group that received RH stimulation.

Table 4.1.

Descriptive statistics for demographic variables.

	RH cTBS			LH cTBS		
	Mean	SD	Range	Mean	SD	Range
Age at time of study	43.59	12.33	27 - 65	43.71	9.00	25 - 58
Education	17.29	3.14	14 - 25	16.71	2.29	12 - 21
Handedness	87.66	15.22	.5 – 1.0	81.59	15.49	.5 – 1.0
Trail Making Test-A (seconds)	25.47	7.38	12 - 43	21.76	4.35	13 - 28
Trail Making Test-B (seconds)	52.12	12.19	27 - 75	47.94	13.17	30 - 78
Digit Symbol Coding (WAIS-III)	84.12	14.35	50 - 108	84.82	13.19	61 - 106
Letter Number Sequencing (WAIS-III)	11.71	1.90	8 - 15	11.71	2.39	8 - 17
Symbol Search (WMS-III)	18.71	3.29	13 - 24	19.06	1.75	17 - 23
Motor Evoked Potential (% output)	54.00	8.67	36 - 67	53.24	7.20	43 - 68
Stimulation Intensity (% output)	47.59	7.78	33 - 57	47.23	6.30	37 - 57
Laterality Index: English	.075	.532	-1.0 - .88	.054	.540	-1.0– 1.0
Laterality Index: Spanish	.344	.622	-1.0– 1.0	.598	.413	-.25– 1.0
Females/Males	6/11			6/11		

Note. RH, group that received cTBS over Broca's homologue in the RH; LH, group that received cTBS over Broca's area in the LH. All working memory and processing speed measures are reported as raw scores. There were no statistically significant differences across groups for any variable.

Table 4.2

Summary of research design.

Session	Details	Duration (approximate)	Location
Day 1	**Informed consent**	1 hour	Laboratory for Brain Recovery and Function (LBRF), Dalhousie University
	Neurocognitive assessment including cognitive testing and background questionnaires		
	LANGA session 1	1 hour	
Day 2	**LANGA session 2** Review of words learned	1 hour	LBRF
	MRI scan	1 hour	IWK Health Centre
	Structural MRI	5 minutes	
	Spanish Runs (x2)	6.5 minutes each	
	English Runs (x2)		
Day 3	**Pre-TMS Naming Test** (Time 1)	10 minutes	LBRF
	cTBS session	1 hour	
	Delay	10 minutes	
	Post-TMS Naming Test (Time 2)	10 minutes	
	LANGA session 3	1 hour	
	Final Naming Test (Time 3)	10 minutes	

Table 4.3

Average naming scores for English and Spanish at all three timepoints, and average confidence scores during LANGA training sessions.

	RH cTBS			LH cTBS			κ
	Mean	SD	Range	Mean	SD	Range	
English Naming							
Pre- cTBS (Time 1)	79.28	10.70	52 - 94	82.56	5.92	73 - 96	.742
Post-cTBS (Time 2)	78.72	11.24	52 - 94	82.71	7.65	69 - 96	.728
Post-LANGA (Time 3)	78.94	10.86	58 - 94	82.94	7.60	66 - 94	.738
Spanish Naming							
Pre- cTBS (Time 1)	57.38	31.07	11 - 125	54.21	15.56	24 - 75	.789
Post-cTBS (Time 2)	55.08	32.09	11 - 137	54.38	17.80	27 - 95	.700
Post-LANGA (Time 3)	57.61	32.45	7 - 141	55.03	15.31	52 - 94	.746
LANGA Training							
LANGA Session 1	46.45	11.64	8 - 81	48.76	10.63	13 - 75	
LANGA Session 2	48.56	12.21	10 - 78	49.21	10.96	13 - 83	
LANGA Session 3	50.31	10.94	14 - 79	50.37	10.45	17 - 79	

Note. κ, Inter rater reliability. Range reflects the range of scores for all words produced in a single session. Average naming score out of 192 possible points. Confidence scores expressed as percentage.

Table 4.4.

Handedness score, laterality index and stimulation site for cTBS and perceived and actual changes in naming performance in English and Spanish following cTBS.

	Handedness	LI English	LI Spanish	MNI Coordinates			Speed Change?		Accuracy Change?		Actual Naming Change (%)	
				X	Y	Z	ENG	SPN	ENG	SPN	ENG	SPN
RH Stim												
TMS_01	1.00	0.09	0.34	52	30	8					0.00	-1.82
TMS_03	0.63	0.01	0.46	52	24	0					10.90	12.44
TMS_05	0.50	0.20	1.00	44	48	-2	↓	↓	↑	↑	0.36	-13.24
TMS_06	0.83	0.88	-0.10	50	30	-6					3.33	-68.62
TMS_07	0.92	0.31	-0.54	50	28	-8					-3.39	11.89
TMS_08	0.75	-0.94		52	26	0	↓	↓	↑	↑	-2.41	14.63
TMS_14	1.00	0.14	0.07	58	8	16					6.44	65.80
TMS_15	0.83		0.97	58	10	14	↑	↓			2.32	-22.31
TMS_18	1.00	-1.00	-0.05	56	22	22			↑	↑	9.00	4.36
TMS_21	1.00	-0.49		58	10	14		↓			6.39	-13.48
TMS_22	1.00	0.76	0.76	58	12	14	↓		↑		-20.85	43.68
TMS_23	1.00	0.46	1.00	50	20	28					-4.94	-2.95
TMS_25	0.80		1.00	52	24	-4	↓	↑	↑	↑	-0.34	6.80
TMS_28	0.90	0.30	0.15	56	24	10				↑	-1.96	-6.48
TMS_32	0.75	0.29	1.00	62	18	14	↑			↓	-5.94	-11.78
TMS_33	0.75	0.29	1.00	52	26	-2				↓	-10.36	-4.55
TMS_34	1.00	-0.02	-1.00	52	26	18		↑			2.59	10.06
LH Stim												
TMS_02	1.00	0.53	0.25	-44	46	12					0.00	-7.84
TMS_04	.50	-0.66	1.00	-54	26	18					6.85	-21.37

	Handedness	LI English	LI Spanish	MNI Coordinates			Speed Change?		Accuracy Change?		Actual Naming Change (%)	
				X	Y	Z	ENG	SPN	ENG	SPN	ENG	SPN
TMS_09	1.00	-1.00	0.98	-48	34	12				↑	-0.33	30.55
TMS_10	1.00	0.09	0.30	-52	20	18					-2.23	3.02
TMS_11	0.83	0.72		-58	8	12	↓	↓	↑	↑	-20.05	-9
TMS_12	0.75			-58	18	12	↑	↑			8.39	-11.93
TMS_16	1.00	1.00	0.98	-52	18	10					-2.15	-9.96
TMS_17	0.67	0.00	0.76	-58	18	12		↓		↑	5.12	13.76
TMS_19	0.75	-0.58	0.10	-56	18	26	↑				-1.22	2.26
TMS_20	0.74	0.02	0.21	-54	22	22					-12.05	-5
TMS_24	0.81		1.00	-56	14	22		↓		↑	3.48	2.29
TMS_26	1.00	0.36	0.45	-56	16	12	↑			↑	4.94	-2.29
TMS_27	0.92	0.28	0.41	-56	24	10		↓		↑	6.08	70.04
TMS_29	0.71	0.19	-0.25	-58	10	8	↓	↓			-2.13	20.78
TMS_30	0.65	-0.01	0.78	-54	22	20		↓		↑	-8.97	-36.50
TMS_31	0.67	-0.18	1.00	-54	20	-4	↑				10.39	-8.67
TMS_35	0.89		1.00	-54	20	26		↓		↑	9.45	7.55

Note. LI, Laterality index; RH Stim, group that received cTBS over Broca's homologue in the RH; LH Stim, group that received cTBS over Broca's area in the LH; Hemi, hemisphere; MNI coordinates represent the highest probability voxel after transformation of the ROI to standard space. Arrows (↑, ↓) represent either a perceived increase or decline in either speed or accuracy respectively based on participants' responses to qualitative questions. Percent change in naming score was calculated using the following formula [(pre-TMS – Post-TMS / pre-TMS) * 100].

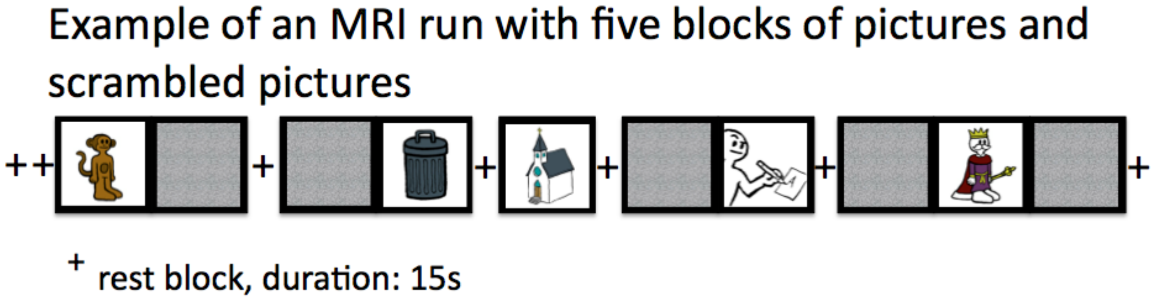

Figure 4.1. Example of an MRI run for both Spanish and English picture naming. Each run began with a rest block and was followed by 5 picture naming, 5 scrambled, and 4 additional rest blocks that were presented in a randomized order, followed by a final rest block. Pictures shown are from a Spanish naming run.

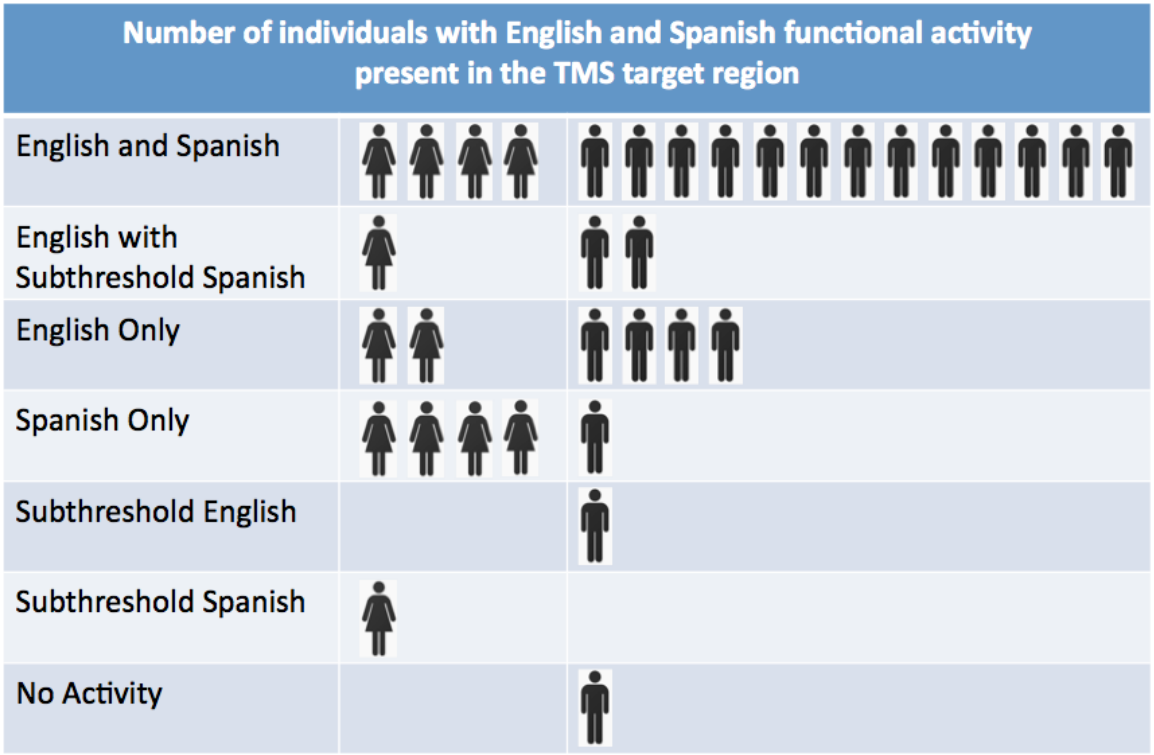

Figure 4.2. The proportion of men and women who demonstrated functional activity in English and/or Spanish in the target region selected for cTBS. Functional activity was identified using a cluster threshold of Z > 2.3 and a corrected cluster significance threshold of $p = .05$, subthreshold activity was identified using a cluster threshold of Z > 2.3, uncorrected.

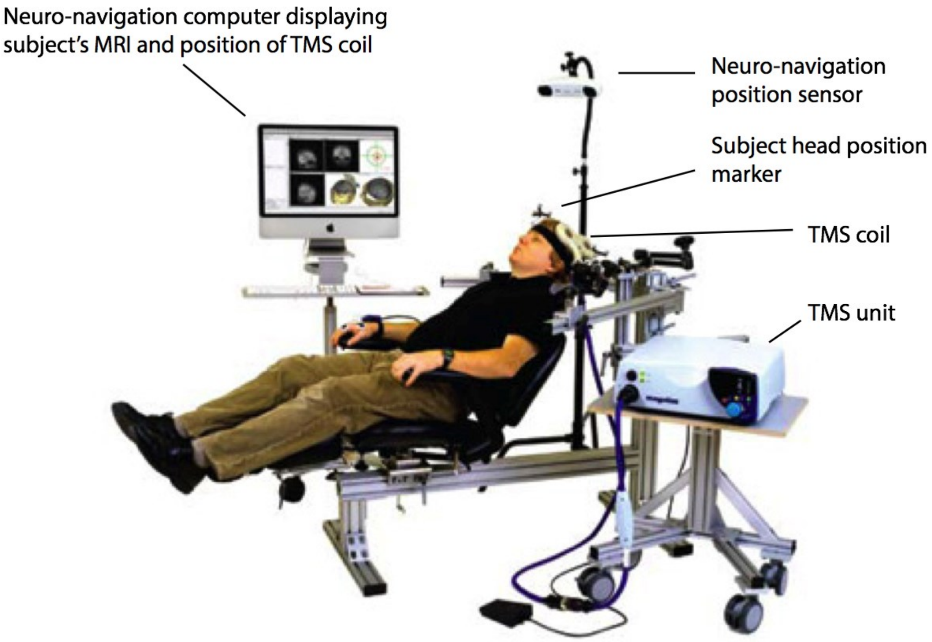

Figure 4.3. Experimental set-up of the TMS system with neuro-navigation.

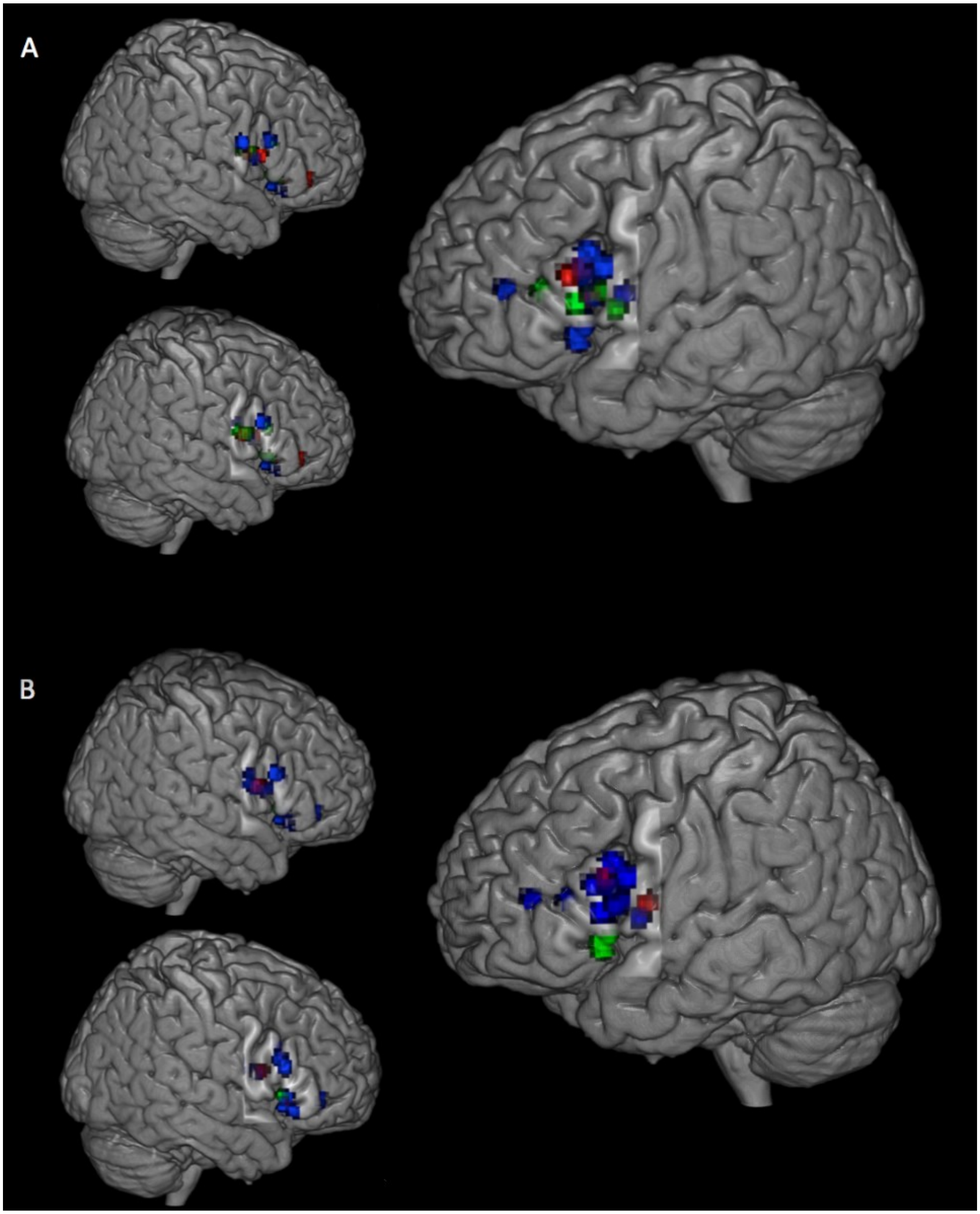

Figure 4.4. Visual depiction of MNI coordinates of TMS targets for all participants. A) shows targets colored according to the percent change in pre- to post-TMS Spanish naming score and B) shows targets colored according to the percent change in pre- to post-TMS English naming score. Targets presented in blue represent no change in

naming score following TMS (± 10%), targets in green represent an improvement of greater than 10%, and targets shown in red represent a decline greater than 10%. *Note.* Colored targets are intended to be purely informative with regard to variability of stimulation site and naming performance following cTBS. Colors do not represent statistically significant differences across participants.

Due to variable depth of target after linear transformation to MNI space, not all stimulation sites in the right hemisphere are clearly visible in one plane, note that in both A) and B) targets in the top image are overlaid on the bottom image.

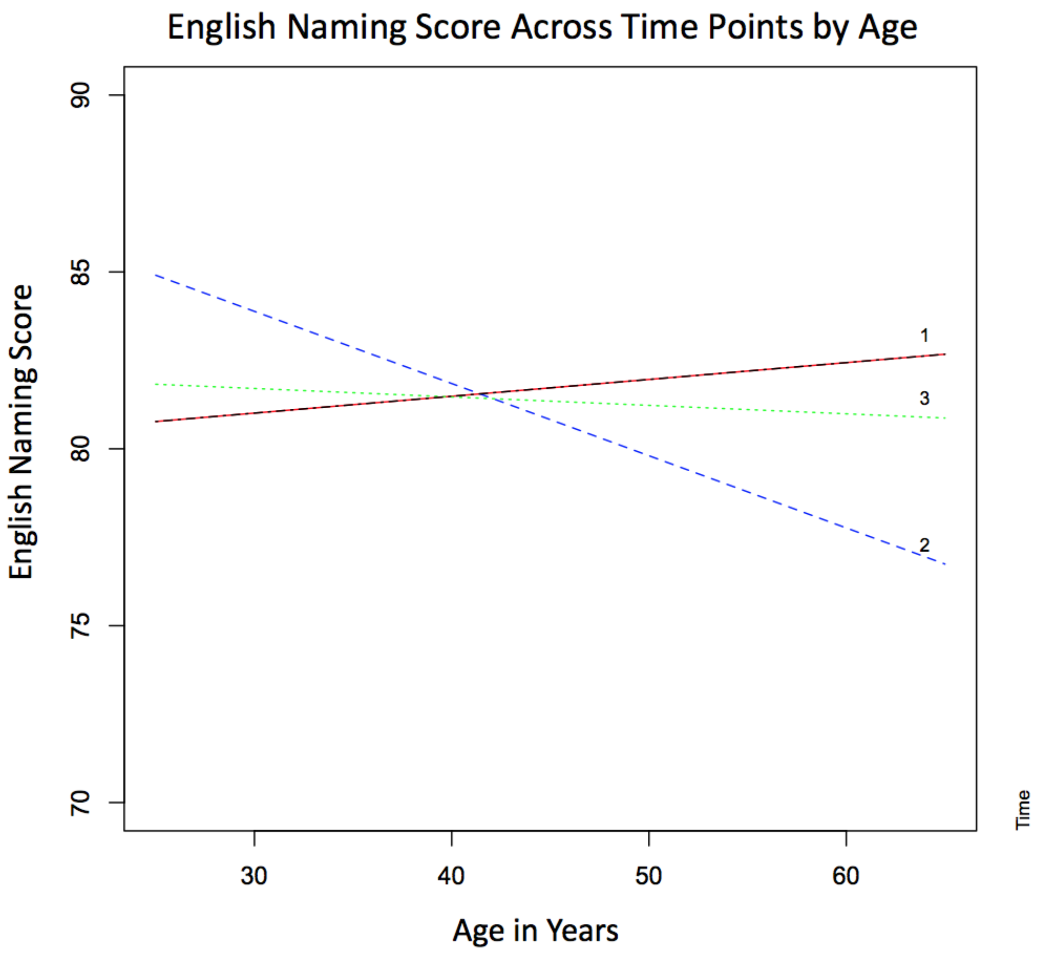

Figure 4.5. Interaction between age and time of testing for English naming performance (scored out of a possible 96 points).

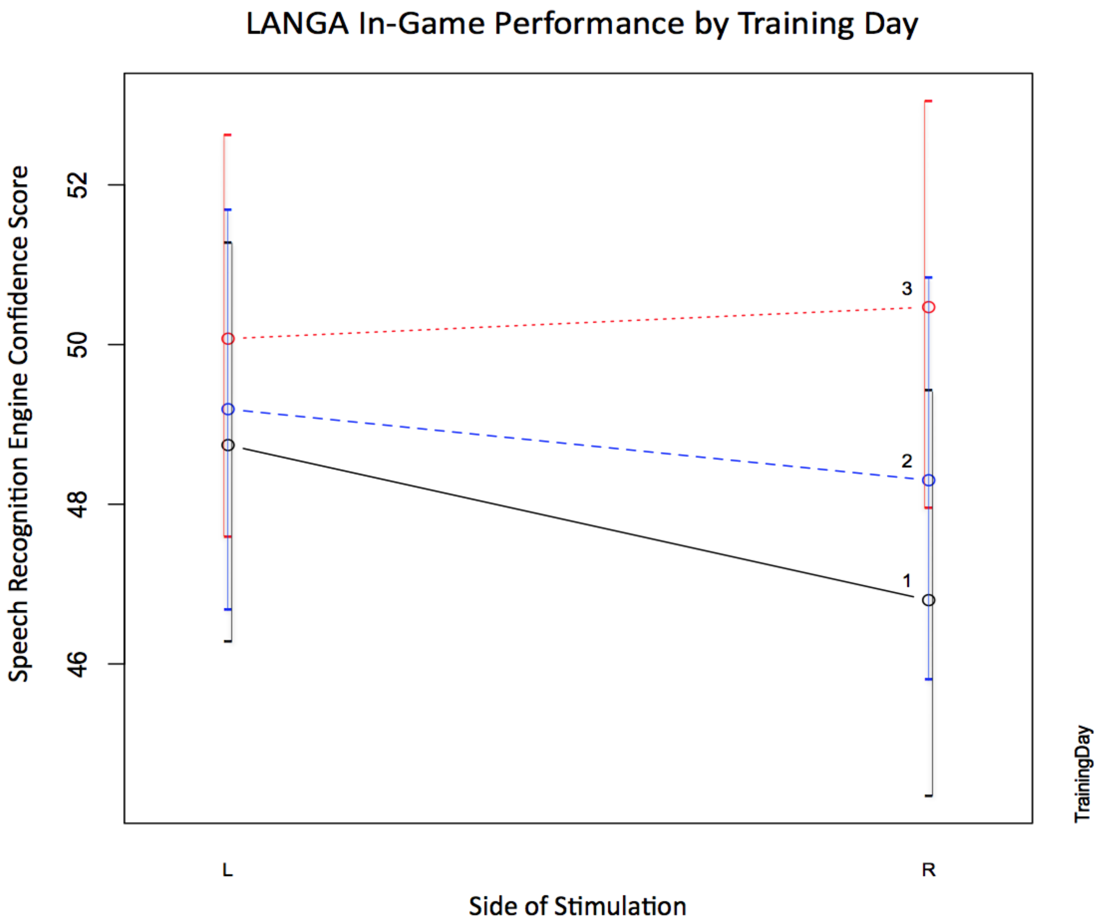

Figure 4.6. Average confidence scores (expressed as a percentage) obtained via speech recognition software during LANGA training sessions 1, 2, and 3 for each group.

CHAPTER 5 DISCUSSION

5.1 DISCUSSION OVERVIEW

The purpose of this dissertation project was to develop a model of effortful lexical retrieval and articulation to simulate aphasia following stroke in order to better understand what has been proposed as compensatory activation of the RH during recovery. In this respect, my research questions were threefold: Firstly, are people able to learn novel second language (L2) vocabulary using a brief computer-based language-training paradigm, and does this new learning represent effortful lexical retrieval and articulation? Secondly, does the effortful lexical retrieval and articulation of newly acquired words in L2 result in right hemisphere (RH) brain activity that can be classified as compensatory, that is, not associated with normal language production? Thirdly, does the application of cTBS to areas of language-based activation in either the RH or left hemisphere (LH) affect expressive speech in English or Spanish during a picture naming task, and following the application of cTBS, is there any effect on further Spanish language acquisition?

The specific hypotheses, methods, and results of these three aspects of this dissertation are described in detail in the preceding chapters. This discussion chapter will provide an overview of the manuscripts presented in this thesis and integrate findings across manuscripts. This chapter will also review strengths and limitations of this work as a whole, and provide a discussion of potential implications of these findings for future research on L2 learning, cortical involvement of L2 processing, and treatment of aphasia.

5.2 EFFORTFUL LANGUAGE PRODUCTION FOLLOWING COMPUTER-BASED L2 VOCABULARY LEARNING

The first manuscript in this thesis project investigated the efficacy of a computer-based language-training program for the acquisition of novel Spanish vocabulary in adults with no prior exposure to Spanish. Although all of our participants were able to learn some words in Spanish, there was a great deal of variability in learning across participants, with total picture-naming scores ranging from 20 to 139 of a possible 192 points. Given the very high number of responses that received an imperfect word score (i.e. 1, 2, or 3 out of 4), it seems reasonable to conclude that our participants found it a challenge to retrieve and say these words in Spanish; thus, it appears that L2 word production may be a good model of effortful lexical retrieval and articulation. However, based on the very large number of non-responses or words that received a score of 0, we can also conclude that our participants were unable to learn many of the words well enough to even attempt to pronounce them. For this reason, the level of overall engagement in speaking tasks may have been insufficient to fully parallel the effect of effortful pronunciation for well-known language, such as we are likely to see in individuals with Broca's aphasia who experience difficulty speaking words in their first language, which is well known and readily understood.

Although prior research has demonstrated that more extensive cortical networks are active during L2 than L1 production in low-proficiency bilinguals (Briellmann et al., 2004; Golestani et al., 2006; Raboyeau et al., 2004, 2008), our participants did not demonstrate this pattern. It is possible that the brief exposure to Spanish provided in this study did not result in sufficient familiarity with the new words to elicit a model in which effortful pronunciation was possible for all of the words presented. Thus, a protocol in which participants are able to attain a higher level of L2 vocabulary knowledge prior to undergoing fMRI and TMS may represent a more accurate model of effortful pronunciation, as seen in individuals with aphasia.

Furthermore, it may be problematic to generalize from our findings to language recovery following stroke as there are likely very different mechanisms associated with learning novel words in a L2, and re-learning vocabulary after cortical damage. According to Jiang's (2000) psycholinguistic model of L2 vocabulary acquisition, novel L2 words are initially learned as formal entities, in which meaning is provided by an external source rather than extracted by the learner. Thus, formal features of the new words, such as phonological and orthographic information may be more salient than semantic content initially, and only later in the learning process, when exposure to the L2 increases, are semantic associations strengthened (Jiang, 2000). In contrast, in L1 development, language is acquired concurrently with the acquisition of meaning. Thus, language recovery following stroke likely involves reorganization of preexisting, but interrupted language networks, with language based on previously developed, strong semantic associations (Musso et al., 1999; Rosen et al., 2000; Saur et al., 2006), rather than reliance on in-tact neural circuitry for novel phonological and semantic processing.

5.3 FIRST AND SECOND LANGUAGE PROCESSING IN THE BRAIN

Consistent with research that has demonstrated a single neural representation for language in the brain (Chee, Tan, & Thiel, 1999; Chee, Caplan, et al., 1999; Klein, Zatorre, et al., 2006; Klein, Milner, Zatorre, Meyer, & Evans, 1995; Klein, Milner, Zatorre, Zhao, & Nikelski, 1999; Klein, Zatorre, Milner, Meyer, & Evans, 1994; Liu, Hu, Guo, & Peng, 2010; Rüschemeyer, Zysset, & Friederici, 2006; See Abutalebi & Chang-Smith, 2013 and Indefrey, 2006 for reviews), in the present study we did not see RH cortical activity that can be convincingly classified as compensatory. In fact, although there was considerable overlap in active brain regions of the LH during L1 and L2 picture naming, the activity present during L2 naming was actually less extensive than in L1, particularly within RH language homologues.

Literature on first and second language processing in the brain is comprised of three main camps of research: Those who support the theory that L1 and L2 are processed by different cortical networks (e.g. Kim, Relkin, Lee, & Hirsch, 1997; Raboyeau et al., 2004; Ullman, 2001); those who support the theory of a common, left lateralized language network for both L1 and L2 (e.g. Chee, Tan, et al., 1999; Chee, Caplan, et al., 1999; Klein et al., 2006, 1999); and those who support the existence of a continuum of activation across both hemispheres for language processing in general, which depends partly on handedness (Knecht et al., 2002, 2003; Knecht, Dräger, et al., 2000). Our results may serve to synthesize some of the existing literature on language representation within the brain in healthy individuals. Firstly, although we do see a high degree of overlap between L2 and L1, with early L2 processing mapping onto pre-existing L1 language networks in the LH, in contrast to previous literature that has demonstrated more extensive cortical activity for L2 than L1 processing (Briellmann et al., 2004; De Bleser et al., 2003; Golestani et al., 2006; Raboyeau et al., 2004, 2008; Vingerhoets et al., 2003; Wartenburger et al., 2003), our participants showed less extensive networks for L2 processing. However, in the present study, our participants likely had such low proficiency in the newly learned L2 that the degree of lexical retrieval and articulation was not sufficient to activate the full language network. This likely resulted from poorly integrated phonological and semantic information (Jiang, 2000), as well as a high non-response rate during the Spanish naming fMRI task in our participants. However, considering that Broca's area of the LH was reliably activated during L2 picture naming across our participants, regardless of level of mastery, indicates that L2 may in fact map onto existing cortical language representation.

5.3.1 SUPPORT FOR THE CONVERGENCE HYPOTHESIS

Given the trend toward activation of bilateral language regions of the IFG with increasing Spanish naming proficiency in our participants, combined with research evidence of more extensive cortical representation of L2 than L1 in primary language areas and surrounding tissue (Briellmann et al., 2004; De Bleser et al., 2003; Golestani et al., 2006; Raboyeau et al., 2004, 2008; Vingerhoets et al., 2003; Wartenburger et al., 2003), we suggest that as proficiency in an L2 develops, L2 language activation maps onto cortical networks associated with L1 processing, with the addition of cortical activity associated with cognitive control (Briellmann et al., 2004; Green, 1986; Pillai et al., 2003; Rudner & Rönnberg, 2008), including cerebellar networks (Callan et al., 2003; Klein, Watkins, et al., 2006; Stoodley & Schmahmann, 2009). However, we hypothesize that, consistent with the convergence theory which suggests that L2 acquisition occurs within the developed neural system of L1 (Green, 2003), as the L2 is mastered, cortical activation ultimately converges onto regions of L1 activity (Abutalebi, 2008; Green, 2003; Indefrey, 2006). Further research involving fMRI data of participants along a continuum of L2 proficiency, or a longitudinal study that investigates L2 activity at various points during the acquisition of a L2 would likely demonstrate more conclusively how the brain processes new language learning.

This suggested pattern of change in activity with L2 acquisition is similar to that which has been suggested to occur during stroke recovery. After studying a heterogeneous group of 14 aphasic patients in the acute, subacute, and chronic stages after stroke using fMRI, Saur et al. (2006) proposed a three-phase model of recovery, the first of which involves an initial breakdown of the language system, including preserved, functionally connected regions of the cortex in the RH. The second, subacute phase is characterized by up-regulation of the entire language network, particularly RH language homologues. Lastly, the chronic phase involves normalization of language activity with a re-shifting of language towards LH language areas (Saur et al., 2006). However, this model does not address the question of whether strong RH activation during the subacute phase of stroke recovery represents compensatory functional recruitment or transcallosal disinhibition. Furthermore, the assumption that LH language areas inhibit homotopic RH counterparts in the healthy brain does not seem to account for the occurrence of bilateral language organization in healthy individuals (Breitenstein & Knecht, 2002); and neuroimaging research to date provides little evidence that cortical areas previously unrelated to language processing take over language functioning following LH damage (Saur & Hartwigsen, 2012), or during L2 processing (See for reviews Abutalebi & Chang-Smith, 2013; Indefrey, 2006).

5.3.2 BILATERAL LANGUAGE LATERALITY

Although previous findings of spatial separation in peak cortical activation during L1 and L2 sentence production (Golestani et al., 2006; K. H. Kim et al., 1997) have suggested that different languages may be governed by different cortical areas, these findings may have been due primarily to differences in proficiency and syntactic language structure rather than to language-specific cortex. Our participants also demonstrated spatial separation of peak activity during English and Spanish naming tasks within Broca's area. However, given the substantial differences in proficiency and mastery between these two tasks, we cannot conclude that spatial separation represents different cortical representations for language. In fact, the dichotomy that has been raised in terms of a single vs. separate neural substrate for L1 and L2 processing is likely an oversimplification of a very complex situation. For example, invasive electrical stimulation of the cortex during pre-surgical mapping has revealed that different languages may be selectively disrupted in multilingual speakers (Black & Ronner, 1987; Lucas et al., 2004; Ojemann &

Whitaker, 1978; Ojemann, 1983); however, the high spatial resolution of invasive mapping techniques allows differentiation of smaller, language specific modules distributed within shared language processing regions (Abutalebi & Green, 2008). Researchers have shown using invasive intracortical electrode mapping that the articulation of specific phonemes may occur at the level of the individual or small groups of neurons that are tuned specifically to different aspects of language (Blakely et al., 2008; Ojemann et al., 2009). Thus, as hypothesized by some neuroimaging researchers (e.g. Chee, Soon, & Lee, 2003; Indefrey, 2006; Klein, Zatorre, et al., 2006), the most likely scenario is one in which language specific cortex contains neurons or small groups of neurons that are sensitive to the phonetic, semantic, and syntactical aspects of language, and as well as to different languages. Accordingly, it is reasonable to hypothesize that two words with a common meaning, but that have different linguistic features will activate common cortex for the extraction of meaning, but different regions that are sensitive to linguistic features of language.

In this thesis project, in addition to LH activity, we saw significant RH fMRI activity during English picture naming, a finding that is consistent with those of Knecht and colleagues (Knecht et al., 2002, 2003; Knecht, Dräger, et al., 2000). However, unlike Knecht and colleagues, who found a significant relationship between handedness and language lateralization, we found no such relationship across our participants. Conversely, recent research has indicated that bilateral language functioning may be associated with strong cognitive ability, including verbal comprehension and perceptual organization (Powell, Kemp, & García-Finaña,

2012) and improved performance on a test of language competence (van Ettinger-Veenstra et al., 2010). Considering that participants in the present study scored in the average range or higher on measures of working memory and processing speed, it is possible that bilateral activity during English picture naming tasks may reflect strong L1 verbal abilities in this sample as well, thus, the relationship between language laterality and cognitive functioning, particularly with respect to verbal ability, certainly warrants further investigation.

5.4 TMS OVER BROCA'S AREA AND BROCA'S HOMOLOGUE

Although there is strong evidence that inhibitory rTMS applied over RH language homologues may facilitate recovery of language function in individuals who have aphasia after suffering a LH stroke (Barwood et al., 2011; Kakuda, Abo, Kaito, et al., 2010; Kakuda, Abo, Uruma, et al., 2010; Khedr et al., 2014; Malcolm et al., 2007; Martin et al., 2004, 2009; Naeser et al., 2004, 2010; Naeser, Martin, Nicholas, Baker, Seekins, Helm-Estabrooks, et al., 2005; Thiel et al., 2013; Tsai et al., 2014), the effects of inhibitory noninvasive brain stimulation (NBS) on language functioning in healthy individuals are less clear. Whereas inhibitory rTMS and cTBS have both been found to inhibit cortical activity in the motor cortex in healthy individuals (W. H. Chen et al., 2003; Huang et al., 2005, 2011), with results of cTBS remaining in place for up to 60 minutes, other studies have reported no effects of offline inhibitory rTMS applied to the language cortex on subsequent language processing tasks (Andoh et al., 2006; Hartwigsen et al., 2013; Restle et al., 2012). Other studies have demonstrated a variable effect of cTBS in particular as measured by motor evoked potential (MEP), with up to a 50% non-response rate (Hamada et al., 2013; Vallence et al., 2013). Consistent with these findings, inhibitory cTBS did not produce any significant, consistent effects on picture naming in either English or Spanish, or on Spanish vocabulary learning in this study, irrespective of stimulation side.

Our finding that inhibitory cTBS to either Broca's area or Broca's homologue did not interfere with lexical retrieval and articulation of English or Spanish may be due to facilitatory effects of unaffected tissue following TMS induced lesions. In previous research that paired inhibitory TMS with fMRI, Thiel et al. (2006) reported that inhibitory rTMS over the left IFG in healthy subjects resulted in decreased LH activity, but increased homologous right IFG activity in all subjects. This rightward shift in language activity following a transient virtual LH lesion was initially interpreted as supporting the hypothesis of transcallosal inhibition. However, more recently Hartwigsen et al. (2013) demonstrated adaptive up-regulation of RH language homologues, which in turn exerted a reciprocal, facilitatory influence on LH language regions, which was protective against behavioural deficits following a transient TMS-induced LH lesion. This reciprocal facilitatory influence was interpreted as evidence against the hypothesis of transcallosal inhibition. Thus, inhibitory TMS over LH language regions did not decrease inhibition of RH language homologues, but increased RH activity reciprocally facilitated LH language functioning, which resulted in a small, paradoxical improvement of RT during pseudoword repetition tasks (Hartwigsen et al., 2013). Therefore, it is possible that a similar phenomenon occurred in our participants, in which inhibitory TMS resulted in a decrease of activity over the stimulation site, which prompted a facilitatory drive from the contralateral hemisphere that negated any effects of inhibition. However, as we did not conduct concurrent or post-TMS neuroimaging, it is impossible to conclude whether a lack of effects was due to reciprocal facilitation, non-response, or some other possibility.

5.5 TMS AS TREATMENT FOR APHASIA

The lack of behavioural effects associated with inhibitory cTBS over LH or RH language regions in healthy controls may have important implications in the development of TMS as a treatment for aphasia following LH damage. Traditionally, findings supporting the use of TMS to treat aphasia have been interpreted as supporting the model of transcallosal inhibition (e.g. Fregni & Pascual-Leone, 2007; Kakuda, Abo, Uruma, et al., 2010; Thiel et al., 2006). However, this hypothesis suggests that aphasia would be less likely to occur in individuals such as the participants in the present study, who demonstrated bilateral brain activation during English naming (Knecht et al., 2002). Conversely, RH activity following stroke likely is compensatory, although not in the way of a take-over of language function by previously unrelated cortex (Saur & Hartwigsen, 2012). Rather, aphasic patients may rely more heavily on RH language regions in recovering from a LH lesion that prevents full recovery of both brain hemispheres, through functional recruitment of undamaged cortex that is connected to the language network (Hartwigsen et al., 2013). Thus, inhibitory rTMS over RH language homologues may yet have merit as a treatment for aphasia, though not by the mechanism traditionally assumed. Given findings that inhibition of LH language regions results in up-regulation of RH activity, which in turn reciprocally facilitates affected LH function, effectively preventing behavioural deficits in healthy controls (Hartwigsen et al., 2013), inhibition of RH regions in aphasics may similarly serve as an indirect stimulation of LH regions, rather than as a reduction in maladaptive compensatory activity (which is theorized to inhibit recovery of LH language regions). Thus, the mechanism behind TMS as therapy for aphasia may be that of a facilitation of the LH rather than a constraint of the RH.

5.6 PUTTING IT ALL TOGETHER: THE ROLE OF THE RIGHT HEMISPHERE

Overall, our MRI findings in combination with previous research on cortical representation of language functioning indicate that the RH plays an important role in language processing, both in healthy and aphasic individuals. However, the specific role of the RH may differ across individuals as a function of handedness (Knecht, Dräger, et al., 2000), cognitive functioning (Powell et al., 2012), and verbal ability (van Ettinger-Veenstra et al., 2010); or may reflect extra-linguistic processes such as complex integration of verbal information in working memory (Vigneau et al., 2011). Further research is necessary to fully elucidate the specific functions of the RH in different individuals, whether through high resolution neuroimaging during language tasks that include different components of language processing or by systematic use of inhibitory and excitatory TMS over different, systematically identified targets in the right IFG to determine if any regions are more susceptible than others to stimulation. Furthermore, online paired pulse TMS techniques that simultaneously inhibit homologous regions of the left and right hemispheres may serve to further elucidate the facilitatory and inhibitory interactions among regions of the language network (Rossi et al., 2009).

5.7 SECOND LANGUAGE PROCESSING AS A MODEL FOR EFFORTFUL SPEECH PRODUCTION IN APHASIA

Overall, despite the suggestion that low-proficiency L2 learners may provide a model for the effortful pronunciation that occurs in aphasia (Raboyeau et al., 2008), results of this thesis indicate that L2 acquisition is not a good model for the effortful language processing seen in Broca's aphasia. L2 acquisition in healthy controls seems to occur within the intact language system underlying L1 processing. Thus, the phonological and semantic processing associated with L2, while effortful, is not a perfect model of Broca's aphasia where the problem is primarily with accessing the formal lexical representation of a given word rather than a semantic problem (Le Dorze & Nespoulous, 1989); even with word finding difficulties, the level of familiarity with the language is not comparable. There is some indication that despite difficulties producing a word verbally, individuals with Broca's aphasia still have access to the semantic and lexical representation when asked to write the word (Raboyeau et al., 2008). Although, in the studies by Raboyeau and colleagues, L2 learners were asked to re-learn previously learned L2 vocabulary (Raboyeau et al., 2004, 2008, 2010), which may be a better model of the lexical difficulties seen with Broca's aphasia than the new L2 learning used in this study.

5.8 TMS MAY NOT PROVIDE A VALID MODEL OF APHASIC STROKE

It is generally accepted that inhibitory TMS may create a ‘virtual cortical lesion’ (Pascual-Leone et al., 1991, 2000), and it has been hypothesized that TMS over cortical language regions may mimic the effects of an aphasic stroke (Andoh & Martinot, 2008; Knecht et al., 2002). However, we argue that the cortical inhibition induced by cTBS is not truly comparable to a stroke that results in aphasia, which often damages underlying white matter as well as cortical regions outside Broca’s area (Mesulam, 2000). Rather, the lesion induced by TMS is generally smaller[4] and leaves perilesional regions intact and active, allowing for facilitatory effects within perilesional cortex that may ultimately occur following TMS irrespective of stimulation side (Hartwigsen et al., 2013). For example, in healthy L2 learners, whereas a lack of consistent effects following inhibitory cTBS may have been impacted by either adaptive upregulation or reciprocal facilitation of homotopic language regions, such protective mechanisms may not be available for aphasic patients who receive TMS over the intact RH following a lesion to primary LH language regions. This may, in part, explain why language functioning appears to be modulated more readily, and to a more striking degree in aphasic patients compared to healthy controls.

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[4] It has been estimated that TMS affects a cortical volume of only approximately 1cc (Roth, Saypol, Hallett, & Cohen, 1991; T. A. Wagner, Zahn, Grodzinsky, & Pascual-Leone, 2004)

5.9 LIMITATIONS AND FUTURE DIRECTIONS

There are several limitations to the current work that should be addressed. With regard to L2 training, although we were able to control for the amount of L2 training input that each participant received by designing a study with a constant level of instruction for all participants, we were unable to control for the amount of L2 intake or learning by each participant. Thus, despite a consistent level of L2 exposure and training across participants, our participants demonstrated a range of proficiency in Spanish naming scores. Furthermore, the challenging nature of our language-training paradigm may have prevented optimal MRI and TMS results, as overall vocabulary learning was sub-optimal. Previous research in our lab that has used LANGA, has shown that participants did not have difficulty learning 12 words per day over a period of 8 days, and demonstrated altered EEG response to novel Spanish words following training (Eng, unpublished thesis). Although the present thesis project utilized a condensed paradigm in which participants were asked to learn 24 words per day over 3 days, other studies have reported that participants were able to learn an average of 17 pseudowords per session over three implicit learning sessions (Breitenstein et al., 2004), indicating that our language task should not have been unreasonably demanding. However, not only did the pseudowords contain only two syllables each compared to the 3.40 on average in the present study, but these prior studies both used participants under the age of 32, and who were on average much younger than those in the present thesis project. As the goal of this thesis project was to understand language processes associated with L2 learning, with the ultimate goal of generalizing to research on stroke recovery, efforts were made to recruit adults nearer the average age of stroke survivors. Furthermore, our results revealed that that the ability to learn new words in Spanish through LANGA was negatively correlated with age (r = -.558). Thus the combination of a condensed language-training paradigm, coupled with the use of older participants may have limited the degree to which our participants were able to benefit from Spanish vocabulary training.

In terms of the MRI and TMS portions of this project, there was a clear imbalance in the relative difficulty of the English and Spanish fMRI naming tasks and the naming tests used to assess the effects of TMS. The imbalance in difficulty of MRI tasks prevents firm conclusions regarding differences in cortical activity that are directly attributable to differences in language vs. differences relating to task difficulty. Likewise, given that the majority of our participants performed very well during the English naming tests, there may have been a ceiling effect, in which, although decline was possible following TMS, we were much more limited to detect any potential improvements. Low overall performance on Spanish may have similarly introduced a floor effect on pre-post TMS naming. Thus, there is a need for future studies to consider developing more balanced language tests for L1 and L2 in terms of relative difficulty and cognitive demand to better understand the potential effects of TMS on language functioning.

Additionally, in contrast to research that has investigated brain activity following TMS (Hartwigsen et al., 2013; Saur et al., 2006), this thesis presents no confirmation of the causal effects of TMS – or lack thereof – on brain activity since the costs and time constraints of an additional MRI scan following stimulation were prohibitive. However, future research charting the functional effects of various TMS protocols at various regions of interest within the cortex, in combination with behavioural measures of language functioning would provide valuable insight into cortical networks involved in language processing.

There are also a number of limitations that are inherent to the use of TMS as a research tool. Although functionally guided TMS based on individual patterns of fMRI activation provide a significant advantage over protocols that use anatomical landmarks alone to identify targets (Lucas et al., 2004), across participants functional activity associated with language processing was often widely distributed throughout the brain. In some cases there was a clear focus of activity on the cortical surface that clearly indicated activity in Broca's area. In other cases, primary language activity was located further from the cortical surface or within the insula. Several studies have acknowledged the difficulty in controlling for variable depth of target regions across participants (Andoh et al., 2006; McConnell et al., 2001; Nixon et al., 2004). Consequently, although TMS that is guided by individual functional activity may allow for more precise targeting of regions within Broca's area that are likely to be affected by TMS, we are unable to increase or decrease the level of stimulation to account for target depth. As the field of stimulation drops off further from the cortex, superficial targets are presumably easy to stimulate, whereas those located deeper in the cortex are more challenging and would presumably have a higher stimulation threshold for the effects of TMS to be apparent (Siebner, Hartwigsen, Kassuba, & Rothwell, 2009). Currently, TMS protocols involve using the same threshold – a percentage of each individual's RMT – for all participants in a given study. Although this approach meets current safety standards for the application of TMS (Rossi et al., 2009, 2011; Wassermann, 1998), it is unable to account for variable depth of targets across participants. Thus, a program of research that investigates the effects of different intensities of stimulation at different cortical depths is worth pursuing to provide more information regarding the effects of TMS over specific targets.

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APPENDIX A: SPANISH WORDS, FREQUENCY OF WORD SCORE, AND SYLLABLE COUNT

English Translation	Spanish Word	Word Score and Frequency 0	1	2	3	4	Syllables
Backpacker	El Mochilero	18	7	5	4	0	5
Bear	El Oso	2	0	2	14	16	3
Blackboard	La Pizarra	9	2	14	9	0	4
Brochure	El Folleto	16	6	10	2	0	4
Builder	El Albañil	24	2	4	4	0	4
Building	El Edificio	17	3	8	5	1	6
Buys	Compra	14	2	6	9	3	2
Can	La Lata	6	1	6	9	12	3
Carries	Carga	12	2	5	6	9	2
Church	La Iglesia	8	1	11	13	1	5
Cleans	Limpia	20	3	1	5	5	3
Clown	El Payaso	16	5	7	5	1	4
Cup	La Taza	6	1	4	12	11	3
Diver	El Buzo	6	2	7	13	6	3
Draws	Dibjua	21	6	1	4	2	3
Fights	Combate	2	0	2	14	16	3
Fish	El Pez	0	0	3	21	10	2
Fork	El Tenedor	15	6	7	5	1	4
Fortress	El Alcazar	11	8	9	5	1	4
Garbage can	El Basurero	20	2	10	2	0	5
Hugs	Abraza	8	2	8	11	5	3
Judge	El Juez	22	3	2	4	3	2
Kicks	Patea	10	6	4	7	7	3
King	El Rey	3	1	2	14	14	2
Knocks over	Abate	7	2	4	12	9	3
Looks	Mira	8	3	6	10	7	2
Loves	Ama	4	2	7	6	15	2
Lumberjack	El Leñador	27	3	3	0	1	4
Magazine	La Revista	19	5	4	4	2	4
Monkey	El Mono	6	1	3	13	11	3
Nun	La Monja	12	5	6	10	1	3
Nurse	La Enfermera	15	6	11	1	1	5
Plumber	El Fontanero	13	2	5	6	8	5
Poster	El Cartel	8	5	6	10	5	3
Postman	El Cartero	9	6	10	7	2	4
Priest	El Sacerdote	27	4	3	0	0	5
Raises	Levanta	7	1	6	14	6	3
Reads	Lee	5	2	4	8	15	1
Shakes	Sacude	13	5	6	8	2	3
Shoots	Dispara	7	1	8	13	5	3

English Translation	Spanish Word	Word Score and Frequency					Syllables
		0	1	2	3	4	
Store	La Tienda	17	2	2	8	5	3
Surprises	Sorprende	7	5	8	8	6	3
Teacher	La Maestra	17	5	6	6	0	3
Waitress	La Mesera	12	5	5	9	3	3
Witch	La Bruja	4	3	2	11	4	3
Wizard	El Hechicero	16	5	8	2	3	5
Woman	La Mujer	5	3	10	10	6	3
Writes	Escribe	5	3	10	10	6	3
Total		572	15	27	38	242	

APPENDIX B: ENGLISH WORDS AND SYLLABLE COUNT

English Word	Syllables	English Word	Syllables
Accordion	4	Lobster	2
Anchor	2	Mouse	1
Ant	1	Nut	1
Asparagus	4	Owl	1
Axe	1	Peacock	2
Barrel	2	Penguin	2
Baseball bat	3	Piano	3
Basket	2	Pineapple	3
Bee	1	Pliers	2
Bell	1	Roller skate	3
Bow	1	Rolling pin	3
Butterfly	3	Screwdriver	3
Camel	2	Seahorse	2
Drum	1	Skunk	1
Elephant	3	Snowman	2
Football helmet	4	Spinning wheel	3
French horn	2	Strawberry	3
Frog	1	Swan	1
Giraffe	2	Thimble	2
Goat	1	Tiger	2
Hammer	2	Watermelon	4
Harp	1	Whiste	2
Kangaroo	3	Windmill	2
Lion	2	Zebra	2

APPENDIX C: STANDARD OPERATING PROCEDURE

V 1.0. 11/07/2012 1

LABORATORY FOR
BRAIN RECOVERY AND FUNCTION
SCHOOL OF PHYSIOTHERAPY
DALHOUSIE
UNIVERSITY
Inspiring Minds

Standard Operating Procedure: transcranial magnetic stimulation (TMS)

Purpose: This standard operating procedure describes the procedures for the use of transcranial magnetic stimulation (TMS) equipment.

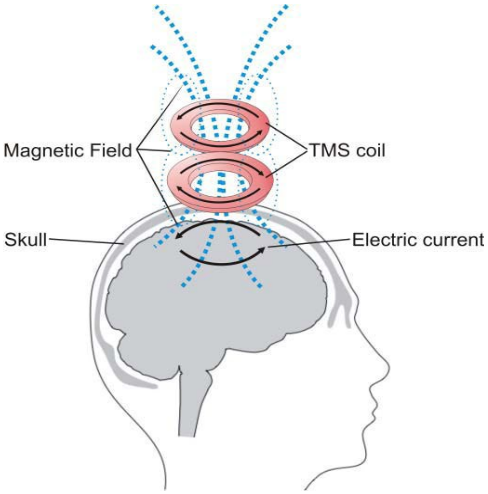
Responsibility: Faculty researchers or supervisors, undergraduate and graduate students

1.0 Background

Transcranial magnetic stimulation (TMS) has been used in a growing number of laboratories worldwide since 1985. TMS is a widely used technique that excites cortical tissue in humans for both experimental and clinical purposes. TMS involves using a series of brief magnetic pulses applied on the outside of the head over cortical regions of the brain. Briefly, TMS relies on the properties of electromagnetic induction; a rapidly changing magnetic field is generated when a high-voltage current is passed through a coil. When this coil is held in close proximity to any electrically conducting medium, such as the brain, this time-varying magnetic field induces current in a direction opposite to the original current in the coil (**Figure 1**).[1,2] TMS can be applied one stimulus at a time, single-pulse TMS, in pairs of stimuli separated by a variable interval, paired-pulse TMS, or in trains, repetitive TMS (rTMS). Single-pulse TMS can be used, for example, for mapping motor cortical outputs, studying central motor conduction time, and studying causal chronometry in brain-behavior relations. In paired pulse techniques TMS stimulation can be delivered to a single cortical target using the same coil or to two different brain regions using two different coils. Paired pulse techniques can provide measures of intracortical facilitation and inhibition, as well as study cortico–cortical interactions.3

Below is a point-by-point description of the procedure.

Figure 1. Schematic of current flow direction in a magnetic coil and the induced current in the brain



2.0 Determining the Resting Motor Threshold using Single Pulse Transcranial Magnetic Stimulation

2.1 Using the neuronavigation system pre-loaded with the participants anatomical MRI, position the TMS stimulation coil over the ‘hand knob’ region of the primary motor cortex of the hemisphere desired for stimulation [this location approximates the C3 position on the international 10-20 system for EEG (i.e., 50% of the measured distance between the vertex of the head and the left preauricular point)].

2.2 Starting at 30% of the stimulator output, deliver single TMS pulses while monitoring for (a) participant sensation of the stimulus in a target muscle and (b) the occurrence of a motor evoked potential (MEP) in a target muscle of the right hand or forearm.

2.3 If the single TMS pulse does not elicit a MEP/sensation then reposition the stimulation coil 0.5 cm anterior; if the MEP/sensation is still absent, move the coil 0.5 cm to the left or right as required. The effect of stimulation will be re-checked at each new position using the same stimulus intensity. If no suitable location elicits a response then the process will be repeated using greater stimulus intensity.

2.4 Increase the stimulus intensities in steps of 5% until a MEP can be seen. The objective here is to locate the motor ‘hotspot’ for the target muscle (the predominant motor cortical representation controlling the target muscle). This motor ‘hotspot’ is the location that yields the largest MEP amplitude using the minimal necessary stimulator intensity.

2.5 Determine the resting motor threshold (RMT) at the motor ‘hotspot’. Increase or decrease the stimulus intensity until a MEP (of at least 50 μV) can be seen on 5 of 10 trials of stimulation on the motor ‘hotspot’.

2.6 For muscles of the hand and forearm, MT is usually in the range of 45-60% of the maximum stimulator output with a 70 mm typical figure-of-eight coil; if MT is not evident before increasing the stimulus intensity to 70% of the maximum stimulator output, stop the experiment.

3.0 Performance of Repetitive Transcranial Magnetic Stimulation (rTMS)

3.1 The RMT determined in section 2 above will be used to guide the stimulus intensity for 1 Hz rTMS.

3.2 Localization of target sites will be determined based on the objectives of the study. In most cases, the location of target sites will be determined using a participant’s anatomical or functional MRI co-registered with the neuronavigation system. Use of the neuronavigation system to guide the position of the stimulator coils provides the ability to focally stimulate (on the order of millimeters) a given region of the brain.

3.3 A computer program will control the timing of the rTMS application such that stimuli will be applied using a research ethics board (REB) approved stimulation paradigm that meets consensus guidelines for the safe application of TMS.3 A typical stimulation paradigm used in rTMS studies includes stimulation at 1 Hz or lower with the intensity of stimulation not to exceed 140 % of an individual’s RMT (see figure 2 below).

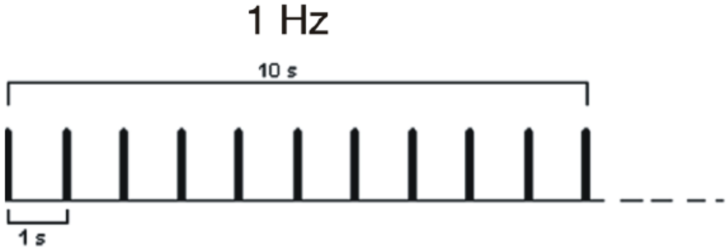


Figure 2. Example of 10 s of rTMS at 1 Hz.

4.0 Description of rTMS Procedure for Research Participants

The following information will be provided to research participants in the informed consent letter:

“As a participant in this study, rTMS will be used to stimulate different regions of your brain. rTMS involves delivering brief magnetic pulses over different locations on your head. You will be asked to keep your head as still as possible. rTMS uses a magnetic stimulator which is basically a set of electrical capacitors that can store and rapidly discharge electricity into a coil of electrical wires that are encased in plastic. The plastic case rests against your head. As electrical current flows through the coil, a magnetic field is generated that passes through the skull and induces a second electrical flow of current in the brain that persists for a very brief time (< 1 second).

This procedure is not painful. You will hear a clicking noise as the current flows through the coil and may experience involuntary activation of different muscle groups depending on the position of the coil over the head. You may also feel some tingling sensations on the head where the TMS coil is located. Ear plugs will be provided during stimulation for added comfort. We will first determine the location within the motor cortex that evokes a muscle response. We will then determine the minimum amount of brain stimulation necessary to evoke that response."

5.0 Description of Risks Associated with Use of rTMS for Research Participants

The following information will be provided to research participants in the informed consent letter:
A series of adverse effects that can be induced by TMS have been identified. However, there is no evidence that the procedure is harmful if appropriate guidelines are followed.3,9,10

The following are ***risks and discomforts*** *that are possible when undergoing rTMS and are communicated in writing to participants in the informed consent document:*
a) The procedure is painless, although it can cause muscles to contract immediately after stimuation, which may lead to residual soreness caused by muscle fatigue over the duration of the experiment.
b) Approximately 1 in every 10 research participants undergoing TMS experience headaches or dizziness, which are believed to be due to excessive muscle tension. In the case of a headache, you will be advised to take whatever pain medication you usually take for mild headaches, which in most cases promptly resolves the discomfort (for example acetaminophen promptly resolves the discomfort in most cases).
c) Approximately 1 in every 100 research participants undergoing TMS experiences neck stiffness and pain. This is believed to be due to the straight posture of the head and neck during the application of TMS. In the case of a headache, you will be advised to take whatever pain medication you usually take for mild headaches, which in most cases promptly resolves the discomfort (for example acetaminophen promptly resolves the discomfort in most cases). Participants are asked to advise the researcher at the first opportunity if they experience any neck stiffness or soreness. In this situation, the participant may opt to withdraw from the study or to rest and change posture for several minutes before the procedures are resumed.
d) TMS produces a loud clicking noise when the current passes through the coil. This loud click can result in tinnitus (i.e., "ringing" in the ears) and temporary decreased

hearing if no ear protection is used. To prevent this adverse effect all research participants receiving TMS and those researchers delivering TMS will be expected to wear earplugs.

e) The use of single, paired pulse, or low frequency (repetitive) TMS has never induced a seizure in a healthy participant. However, there is the possibility that TMS can induce a convulsion even in the absence of brain lesions, epilepsy or other risk factors for seizures. Only 7 cases of convulsions have been reported using single pulse TMS in patients with pre-existing brain damage despite extensive use in both the healthy and patient population. In the case of high frequency repetitive TMS the risk of seizure is reported at less than 1% in healthy young adults and only one seizure has ever been reported in a normal subject following this higher frequency stimulation.3

f) The overall risk for seizures during TMS is thought to be in the order of 1 in 1000 studies. In the event a participant does experience a seizure, emergency services via 911 will be contacted. One member of the research team will stay with the participant at all times. A second member of the research team is responsible for calling emergency services via 911 and then Dalhousie Security (ext 4109) to inform campus police of the location of the incident and facilitate the arrival of emergency personnel.

Pregnancy

Women who are or could be pregnant may not participate in TMS studies because the potential effects of magnetic fields on the fetus are unknown. Study personnel will follow an established protocol in screening women who may be of childbearing age. Briefly, if the potential participant is a female in reproductive years, she must either (a) confirm that she practices an appropriate method of contraception, or (b) have a negative urine pregnancy test to proceed with the MRI and/or TMS session. Appropriate methods of contraception include abstinence, birth control pills or implanted hormonal contraceptives, contraceptive barriers such as a diaphragm or condom, intra-uterine device, and having only partner(s) who have a history of vasectomy.

Adapted from the University of Waterloo Human Research Ethics Committee UWSOP # 214: Protocol for Repetitive Transcranial Magnetic Stimulation (TMS) of the Brain with permission from Dr. M Vesia

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APPENDIX D: EMERGENCY PROTOCOL

V 1.0. 11/07/2012 1

LABORATORY FOR
BRAIN RECOVERY AND FUNCTION
SCHOOL OF PHYSIOTHERAPY
DALHOUSIE
UNIVERSITY
Inspiring Minds

Safety Document: Lab personnel and transcranial magnetic stimulation (TMS)

Purpose: The purpose of this document is to outline the policies in place to ensure the safe operation of TMS by lab personnel. Additionally, a standard operating procedure is described in the rare instance that an emergency situation occurs.

Responsibility: Faculty researchers or supervisors, undergraduate and graduate students

1.0 General

Transcranial magnetic stimulation (TMS) may only be performed by lab personnel or associated investigators who have the following:

I. First responder certification a. This includes a current certificate in first aid and CPR from a recognized institution (e.g., Heart and Stroke, St. John's Ambulance)

II. Completion of a TMS training module, which includes: a. Familiarity with the safe operation of the TMS hardware and software i. Computers
  ii. Trigger cables
  iii. TMS unit front panel, amplifiers, coils and where applicable the neuronavigation unit (Brainsight 2)

   b. Have read and reviewed pertinent literature related to the safe operation and application of TMS (e.g., International Consensus Guidelines first published by Wasserman 1998 and updated by Rossi et al., 2009). This literature is available electronically (PDF) and in hard copy in the Laboratory for Brain Recovery and Function
   c. Have read and reviewed the Laboratory standard operating procedure for TMS

III. Have a study protocol with current approval from an affiliated research ethics board (which includes the Capital District Health Authority REB, IWK Health Centre REB or the Dalhousie University REB)

2.0 TMS Procedures

I. TMS Screening Form

For all subjects, the TMS screening form must be completed and signed prior to participation in any protocol using TMS. As per international consensus guidelines,1, 2 an affirmative response ('yes') to one or more of the questions does not represent an absolute contraindication to TMS, however the risk/benefit ratio to participation should be considered by the Principal Investigator. Note that an affirmative response to question #6 (regarding pregnancy) requires investigators to obtain further information (see SOP for TMS section 5.0). If a participant is engaged in subsequent studies, a new form must be completed.

II. Earplugs

All participants (study subject and members of the research team) must wear protective earplugs throughout the duration of the TMS procedures

III. Study personnel present during TMS

There must be a minimum of two lab personnel or associated investigators (who meet the criteria listed above) present during any TMS procedure.

IV. Response to an emergency situation

While a seizure has never been reported with single pulse or repetitive TMS (at low frequency) using healthy subjects, the lab personnel and/or associated investigator must be familiar with the Lab Policy for a seizure, which is outlined below:

i. One of the two investigators will remain with the study participant at all times while the other 1) calls 911 for emergency assistance; and 2) contacts Dalhousie security services at extension 4109 Dalhousie Security (ext 4109) to inform campus police of the location of the incident to facilitate the arrival of emergency personnel.

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