Using MRI functional and structural connectivity patterns as neural biomarkers for predicting specific aspects of second-language learning success

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Abstract

The ability to communicate in multiple languages is increasingly important in a more globalised and connected world. During normal development, learning a first language is generally a natural and effortless process. However, acquiring a second language (L2), especially in adulthood, is often considerably more difficult, leading to varying degrees of success. One factor that can explain this range of outcomes is the variability in individual language learning abilities, though little is known about what leads to this variability. This dissertation aimed to explore how brain organisation contributes to differences in language learning abilities by identifying patterns of anatomical and functional connectivity in the brain that can predict L2 learning aptitude. To this end, the studies made use of a longitudinal design, following 18 participants undertaking approximately 80 hours of training in a French language course and collecting brain imaging data prior to the start of the course, along with fine-grained behavioural measurements related to the participants' French proficiency at the start and end of the course. Most studies focus on the role of classic language regions in the left hemisphere, though ample evidence implicates other regions, including right hemisphere language regions in language processing. In addition, there is increasing focus on studying brain connectivity to explore the role of both hemispheres in language, although few studies have focused on interhemispheric connectivity. Therefore, this dissertation aimed to further explore the role of the left perisylvian language network connectivity and its interhemispheric communication in a more anatomically precise way, using magnetic resonance imaging (MRI) measures to determine anatomical and functional biomarkers for predicting specific types of L2 learning success. The first study used diffusion MRI tractography to examine anatomical brain

connectivity within each hemisphere by measuring microstructural properties of white matter pathways in relation to L2 learning success. We demonstrated a dissociable pattern of predictors within specific frontal and parietal regions, based on intrinsic anatomical connectivity, which was related to distinct, predicted L2 learning improvement. Specifically, we found that stronger anatomical connectivity between area 45 and the angular gyrus (AG) mediated by the second branch of the superior longitudinal fasciculus (SLF II) predicted improvement in lexical retrieval, while connectivity between area 44 and the supramarginal gyrus (SMG) mediated by SLF III predicted improvement in articulation rate. The second study used resting-state functional connectivity (rsFC) measures to examine functional biomarkers of L2 learning success. Intrinsic, interhemispheric functional connectivity was measured between specific regions of interest (ROI). We again demonstrated dissociable patterns of L2 learning predictors, this time based on specific interhemispheric rsFC of selected brain regions relating to the corresponding language aspects hypothesised to improve. We showed that interhemispheric rsFC of areas 44 and 9/46v predicted improvement in sentence repetition, interhemispheric rsFC of area 45 and mid-superior temporal gyrus (mSTG) predicted improvement in auditory comprehension and, finally, interhemispheric rsFC of the AG predicted improvement in reading speed. Taken together, these results further elucidate the neural basis for variability in L2 learning outcomes and indicate that some individuals may have neural connectivity better suited for successful L2 learning.

Résumé

La capacité de communiquer en plusieurs langues est essentielle dans un monde davantage mondialisé et connecté. Au cours d'un développement normal, l'apprentissage d'une première langue est généralement un processus naturel et sans effort. Cependant, l'acquisition d'une deuxième langue (L2), en particulier à l'âge adulte, est souvent plus difficile, conduisant à des degrés de réussite variables. Un facteur qui peut expliquer l'étendue de ces performances est la variabilité des capacités individuelles d'apprentissage des langues, bien que l'on sache peu de choses sur ce qui conduit à cette variabilité. Cette thèse vise à explorer comment l'organisation cérébrale contribue aux différences de capacités d'apprentissage des langues en identifiant des motifs de connectivité anatomique et fonctionnelle dans le cerveau qui peuvent prédire l'aptitude à l'apprentissage d'une L2. Dans ce but, une étude longitudinale a été réalisée, recrutant 18 participants ayant suivi environ 80 heures de cours de français. Des données d'imagerie cérébrale ont été recueillies avant le début du cours, ainsi que des mesures comportementales affinées de la maîtrise du français en début et fin de cours. La plupart des études existantes se focalisent sur le rôle des régions classiques du langage dans l'hémisphère gauche, bien que de nombreuses preuves impliquent d'autres régions, y compris les régions du langage de l'hémisphère droit. De plus, l'étude de la connectivité cérébrale est devenue un axe clé permettant d'explorer le rôle des deux hémisphères dans le langage, bien que peu d'études se soient intéressées à la connectivité interhémisphérique. Par conséquent, cette thèse vise à explorer davantage le rôle de la connectivité du réseau périsylvien gauche et de sa communication interhémisphérique de manière plus précise sur le plan anatomique, en utilisant des mesures d'imagerie par résonance magnétique (IRM) pour établir des

biomarqueurs permettant de prédire des types d'apprentissage de L2 spécifiques. Dans la première étude, la tractographie de l'IRM de diffusion a permis d'examiner la connectivité anatomique du cerveau dans chaque hémisphère en mesurant les propriétés microstructurales des faisceaux de matière blanche en relation avec la réussite en apprentissage de L2. Nous avons montré un motif dissociable de prédicteurs dans des régions frontales et pariétales spécifiques, basé sur la connectivité anatomique intrinsèque liée à un apprentissage distinct et prédit de la L2. Plus précisément, nous avons observé qu'une connectivité anatomique plus forte entre la zone 45 et le gyrus angulaire (AG) par la deuxième branche du faisceau longitudinal supérieur (SLF II) prédit une amélioration de la récupération lexicale, tandis que la connectivité entre la zone 44 et le gyrus supramarginal par SLF III prédit une amélioration de la vitesse d'articulation. La deuxième étude a utilisé des mesures de connectivité fonctionnelle au repos (rsFC) pour examiner les biomarqueurs fonctionnels de la réussite de l'apprentissage de L2. La connectivité fonctionnelle intrinsèque interhémisphérique a été mesurée entre des régions d'intérêt spécifiques. Nous avons également démontré des motifs dissociables de prédicteurs d'apprentissage de L2, cette fois basés sur la rsFC interhémisphérique de régions cérébrales particulières liée aux aspects linguistiques correspondants censés s'améliorer. Nous avons montré que la rsFC interhémisphérique des zones 44 et 9/46v prédit une amélioration de la répétition de phrases, la rsFC interhémisphérique des zones 45 et le gyrus temporal supérieur moyen prédit une amélioration de la compréhension auditive et enfin la rsFC interhémisphérique de l'AG prédit une amélioration de la vitesse de lecture. En somme, ces résultats élucident davantage la base cérébrale de la variabilité de réussite d'apprentissage d'une L2 et indiquent que certaines personnes semblent avoir une connectivité cérébrale mieux adaptée à un apprentissage réussi en L2.

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Now, I can hear the music in the background playing me off stage (I know this isn't the Oscars but it sure feels like it!), so I think it is time to wrap things up. Here is a final thank you to all those that mattered!

Contribution to original knowledge

The present dissertation constitutes original scholarship and makes several distinct contributions to knowledge. The two studies presented are part of only a few studies investigating cerebral connectivity biomarkers of successful L2 learning and extend these existing studies by providing anatomically more detailed and thorough examinations of multiple biomarkers. Moreover, in Study 1, we differentiated the second and third branches of the superior longitudinal fasciculus, which are rarely studied separately, and have not been studied in the context of L2 learning. These findings demonstrate the different roles in language of these two branches of the superior longitudinal fasciculus and highlight the importance of anatomical specificity in language-related studies. Further, in Study 2, we investigated the role of interactions between the hemispheres which are rarely directly studied in the context of L2 learning. These findings establish the importance of considering interactions between the hemispheres in the process of L2 acquisition and demonstrate the functional specificity of the relationship between localised interhemispheric connectivity and language learning outcomes. This work represents a contribution towards understanding the complex interplay between the hemispheres in the context of language learning. Finally, both studies contribute to further our understanding of individual differences in brain connectivity underlying variability in second language learning.

Contribution of authors

II. Study 1 - Frontoparietal anatomical connectivity predicts second language learning success

Authors*: Kaija Sander, Elise B Barbeau, Xiaoqian Chai, Shanna Kousaie, Michael Petrides, Shari Baum, Denise Klein*

I am the primary author of this manuscript. I was involved in study conception and design and applying for ethics, and was the main contributor in participant recruitment, data collection and analysis and writing of the manuscript. Shanna Kousaie assisted with participant recruitment, experimental setup and data collection. Michael Petrides and Elise Barbeau provided anatomical expertise and guidance for the reconstruction of the white matter tracts. Xiaoqian Chai, Elise Barbeau, and Shanna Kousaie assisted with statistical analysis and data analysis. Denise Klein and Shari Baum provided input and guidance at all stages throughout the study, from study conception and design to finalising the results. All authors reviewed and provided feedback on the manuscript.

III. Study 2 - Interhemispheric functional brain connectivity predicts new language learning success in adults

Authors*: Kaija Sander, Xiaoqian Chai, Elise B Barbeau, Shanna Kousaie, Michael Petrides, Shari Baum, Denise Klein*

I am the primary author of this manuscript. I was involved in study conception and design and applying for ethics, and the main contributor in participant recruitment, data collection and analysis and writing of the manuscript. Shanna Kousaie assisted with participant recruitment, experimental setup and data collection. Michael Petrides provided anatomical guidance and expertise. Xiaoqian Chai assisted with the resting-state functional connectivity analysis and statistical analysis. Elise Barbeau, Xiaoqian Chai and Shanna Kousaie provided support with data analysis and statistical analysis. Denise Klein and Shari Baum provided input and guidance at all stages throughout the study, from study conception and design to finalising the results. All authors reviewed and provided feedback on the manuscript.

I. General introduction

Language is arguably the most central and defining element of human society. Communicating using language is a crucial part of everyday life, and the use of multiple languages is becoming more and more necessary in our globalised world. Learning a first language (L1) is a natural and easy process, but acquiring a second language (L2) is notoriously more difficult, particularly later in life (see Long 1990 and Birdsong 2018 for review). There is substantial variability in how well individuals learn a new language (Long 1990; Sparks et al. 1998; Golestani and Zatorre 2009), which is influenced by many factors such as age (Long 1990; Hakuta et al. 2003; Birdsong 2018), mode of acquisition (Freed et al. 2004), and motivation (Schmidt 2001; Masgoret and Gardner 2003). Variability in L2 acquisition is also influenced by natural between-individual differences in language learning abilities (Sparks et al. 1998; Jakoby et al. 2011), though little is known about the factors that lead to those differences. In particular, the factors relating to brain structure and function that may influence individual second language learning skills remain unclear. It is known that language experience and bilingualism can shape brain structure (Klein et al. 2014) and affect how brain networks connect anatomically (Pliatsikas et al. 2015) and functionally (Berken et al. 2016). Previous work has also demonstrated that intrinsic differences in structural (Flöel et al. 2009; Qi et al. 2015) and functional (Ventura-Campos et al. 2013; Chai et al. 2016) connectivity can be predictive of how successful individuals will be in acquiring an L2, thus demonstrating the possibility of relating brain function and structure to L2 learning skills. Furthermore, it is of interest to examine in more depth whether connectivity between specific brain regions can be correlated with particular behavioural improvements in

order to establish functional roles of language-related brain areas in L2 learning. The main question of interest for this dissertation is, therefore, whether specific brain networks involved in language and language learning contribute to variability in L2 learning success; that is, can patterns of structural and functional connectivity be used as markers to predict L2 learning ability? This question is addressed in a longitudinal study of a cohort of 18 participants taking part in a French course. Two studies are presented, which aim to elucidate structural and functional connectivity biomarkers of successful L2 learning in adults, while addressing existing gaps in knowledge and methodology. The following sections outline the main methods enabling us to study brain connectivity in the context of language, the key cortical regions involved in language processing generally, and finally, the brain regions implicated in L2 learning.

I.1. Methods for studying language learning and brain connectivity

The ability to study the underlying brain factors that enable language processing and learning has grown increasingly over the last century thanks to technological advances. A review of the methods developed to study the brain is required to understand how they are applied to elucidate the neural processes underlying language learning. Following early observations relating language deficits to brain lesions (Broca 1861; Wernicke 1874), and the use of electrical stimulation studies in patients undergoing neurosurgery (Penfield and Roberts 1959), the use of Magnetic Resonance Imaging (MRI) has now become one of the most widely-used tools to study brain function and structure (Bandettini 2012; Jones et al. 2013). There are many possible applications for MRI, including several methods that allow us to examine how brain regions connect structurally (Soares et al. 2013) and function together (Eickhoff and Müller 2015;

Soares et al. 2016). In recent years, the focus in studies of the neural correlates of language has moved away from investigating the role of individual brain regions in language processing to understanding how these separate regions interact to give rise to various language processes (Sporns 2011; Li and Grant 2016). Thus, the focus of this dissertation is on the different forms of brain connectivity relating to adult L2 learning, and the section below will outline the principal methods used to investigate second language learning in adults, including structural and functional connectivity.

I.1.1. Methodological considerations for studying second language learning

Several methodological aspects must be considered in studying L2 acquisition. One of these considerations includes how to measure the extent of learning that has occurred. Firstly, this requires defining the behaviour to be measured, which in the case of L2 learning would be proficiency in the language being learned. Proficiency is a broad term and, in the context of L2 language studies, "refers to the extent to which L2 learners master the second language at definite points in time" (Rastelli 2018). Given that the measurement of proficiency in L2 studies can be carried out in a variety of ways, this can be problematic (Rastelli 2018). For this dissertation, the focus is on using psycholinguistic measures that tap into specific language processes and thus measure specific aspects of language. Secondly, in order to quantify learning, data on L2 proficiency must be collected prior to the start of the learning process and after a sufficient period of learning has occurred, in order to look at the differences between time-points. This in turn means using longitudinal study designs, so that data on the same participants can be collected over time (Osterhout et al. 2006; Andrews et al. 2013). This is a

crucial point, as many studies of second language acquisition use cross-sectional designs to compare bilinguals with varying degrees of L2 experience with monolinguals (Legault et al. 2019), with comparatively few studies tracking behavioural changes during the L2 learning process. In addition, a number of the existing studies of L2 learning use short-term laboratory training paradigms, measuring learning over a single session (Golestani and Pallier 2007; López-Barroso et al. 2013; Ripollés et al. 2014). In contrast, longitudinal studies of L2 learning can inform us about the different processes and factors influencing the various stages of longer-term L2 acquisition.

Another methodological consideration is the enormous variability present in terms of L2 learning abilities and outcomes in adulthood. Indeed, compared to L1 studies where the large majority of individuals will reach similar proficiency levels, L2 studies of adult learners will likely show a variety of outcomes. Therefore, focus on individual participant L2 learning success might be more informative than looking at group performance, allowing more fine-grained analyses (Leeser 2013; Qi and Legault 2020). Indeed, in the context of L2 learning studies, participants are often grouped into “successful” vs “less successful” learners (Wong et al. 2007; Mei et al. 2008; Yang et al. 2015). As reviewed by Kanai and Rees (2011), many MRI studies across domains focus on comparing experimental conditions or groups, thus missing the opportunity to relate human behaviour and cognition to underlying brain structure. Thus, an approach taking individual differences into account would relate differences in brain activity, structure, and connectivity with differences in language learning abilities (Qi and Legault 2020). In addition, many studies of L2 learning only acquire data on the trained language (Veroude et

al. 2010; Wong et al. 2011; López-Barroso et al. 2013; Qi et al. 2015), without measuring performance in the L1 to ensure that effects are specific to the L2 and that changes are only occurring in the trained language.

Finally, the type of language training and learning environment must also be considered. Many studies use laboratory-based training paradigms and focus only on a specific aspect of language learning, such as phoneme discrimination (Golestani et al. 2002; Ventura-Campos et al. 2013) or novel word learning (Veroude et al. 2010; López-Barroso et al. 2013); some even use artificial language paradigms (Mei et al. 2008; Flöel et al. 2009; López-Barroso et al. 2013). However, more naturalistic, holistic, and ecologically valid data are also needed to obtain a fuller understanding of second language learning (Andrews et al. 2013).

To address some of these issues, the current project relies on a longitudinal study design, measuring a range of language proficiency measures to examine individual L2 performance in a natural second language adult learning context (i.e., classroom language immersion over a length of time).

I.1.2. Structural connectivity

Now that some of the issues that need to be considered with respect to measuring L2 learning have been described, another area of focus is that of the methods used to measure connectivity in the brain that enable us to study the neural mechanisms through which such learning may occur. With regard to brain structure, information is carried through the brain via

myelinated white matter (WM) pathways. Early information about these structural pathways came from post-mortem human brain dissections (Reil 1809; Gall 1818; Dejerine 1895). The only currently available method to study anatomical connections in vivo in the human brain is diffusion MRI (dMRI), a technique that relies on the diffusion of water molecules to infer information about the microstructure of tissue around which the water moves. This information can be used to infer the orientation of the white matter tracts in the brain, as water flows parallel to the fibre bundles but not perpendicularly; the orientation information, in turn, can be used to reconstruct the anatomical pathways in a process called tractography (Behrens et al. 2014). Once the WM tracts have been reconstructed using tractography, several diffusion measures can be obtained to inform us about the WM microstructure of the tracts and can be used alongside other measures such as behaviour in further analyses. The most common of the diffusion measures is Fractional Anisotropy (FA), which is a measure of the directionality of water diffusion varying between 0 and 1 (Pierpaoli and Basser 1996). Unrestricted diffusion of water molecules, i.e. equal diffusion in all directions, is said to be isotropic and will have FA values close to 0, while highly directional diffusion (if restricted by WM pathways, for instance) is said to be anisotropic and will have FA values close to 1 (Smith et al. 2014). However, diffusion measures including FA do not directly measure a specific WM characteristic or property (such as, myelination, axon diameter, fibre density or fibre organisation), and therefore reflect several WM properties. Interpreting the precise biological meaning of these measures is difficult and remains a matter of debate (Beaulieu 2002; Beaulieu 2014). In addition, dMRI only allows for indirect observation of white matter tracts and tractography presents challenges associated with separating different tracts and establishing

the precise origin and termination of the tracts (Martino et al. 2011; Campbell and Pike 2014). The gold standard for elucidating the white matter connectivity of the brain remains the use of autoradiographic tracers in the macaque monkey (Petrides 2014a). Indeed, this method allows for the precise determination of the origin, course and terminations of the axons that constitute the WM tracts. Although macaque monkeys do not communicate through language in the same manner as humans, cytoarchitectonic studies have shown that they do possess brain areas homologous to human language areas (Petrides and Pandya 2002; Petrides et al. 2005). Thus, tracer studies in monkey models are relevant to the investigation of human brain anatomy, even in the context of language. In conclusion, the ideal way to study WM connectivity in the human brain, which was implemented in this dissertation, seems to be by using a priori knowledge of exact anatomical connectivity in nonhuman primate brains as a reference to inform diffusion studies in humans.

I.1.3. Functional connectivity

Functional MRI (fMRI) is one of the most popular methods for studying brain function and is based on the idea that levels of blood oxygenation vary with brain activity. These changes are reflected in the fMRI signal, since the signal decreases when blood is deoxygenated and increases when it is oxygenated. Changes in blood oxygenation occur when activity increases in a particular brain region and neurons consume the oxygen available, leading to a decrease in oxygenated blood, followed by an increased supply of oxygenated blood to that area (Bandettini 2012). Thus, it is said that fMRI measures the blood oxygenation level dependent (BOLD) signal (Ogawa et al. 1990). Spontaneous BOLD fluctuations also occur at rest, when the

brain is not performing a task (Biswal et al. 1995) and are thought to reflect intrinsic properties of the brain (Fox and Raichle 2007). Such data can be acquired during resting-state fMRI scans when subjects are instructed to simply rest (Lv et al. 2018). Brain areas that are anatomically separated but whose BOLD signals are temporally correlated are said to be functionally connected (Friston et al. 1993), as it is considered that if their activity is consistently correlated then they are part of the same network. Thus, fMRI scans taken at rest can be used to explore resting-state functional connectivity (rsFC) and inform us about intrinsic networks of functionally-communicating brain regions. However, because rsFC is simply a measure of the correlation between the activity of brain regions, one cannot conclude that there is a causal or direct link between the regions. Thus, similar to structural connectivity measured by tractography, the biological basis of resting-state functional connectivity is difficult to interpret (Eickhoff and Müller 2015). Despite this, rsFC remains a useful method, thanks to the low task demands on participants and the ease of acquisition and analysis due to the lack of task constraints to take into consideration. In the context of this dissertation, rsFC is an ideal method to establish individual pre-existing patterns and characteristics of coupling between specific brain regions, and then establish how this coupling may be related to behaviour.

I.1.4. Structure-function relationships

Both structural and functional connectivity measures, such as those previously described, provide useful information concerning the pathways and networks in the brain, though there is not always exact alignment between the two types of measures. The transfer of information between brain regions (i.e. function) is dependent on the connections between those brain

regions (i.e. structure, Honey et al. 2010; Fjell et al. 2016), but specific methods of measuring these types of connectivity do not seem to capture this relationship fully. Several studies have shown strong agreement between rsFC, and anatomical connectivity measured by diffusion imaging (Skudlarski et al. 2008; Greicius et al. 2009; Eickhoff et al. 2010; Hermundstad et al. 2013)**.** However, strong agreement does not mean perfect correspondence between anatomical and functional connectivity, and these studies also note discrepancies between the measures (Skudlarski et al. 2008; Greicius et al. 2009; Eickhoff et al. 2010). Moreover, several studies report a lack of direct relationship between rsFC and underlying structural connections (Koch et al. 2002; Fjell et al. 2016; Tsang et al. 2017). This can be explained by the fact that rsFC between two regions could be mediated by direct anatomical connections, but also by additional indirect pathways through other cortical regions or even subcortical structures. Thus, functional connectivity can exist without direct structural connections (Vincent et al. 2007; Honey et al. 2010; Eickhoff and Müller 2015).

In recent years, there has been a shift towards understanding the brain from a network perspective rather than elucidating the roles of individual regions (Sporns 2013; Eickhoff and Müller 2015; Li and Grant 2016). The brain is a network of distinct but connected regions (Sporns 2013; Pessoa 2014). Therefore, gaining a full understanding of how processes arise in the brain requires understanding the roles of individual brain regions, how they are connected and work together and how this gives rise to various functional processes. Thus, in the context of this dissertation, we were not only interested in studying brain connectivity in relation to L2

learning outcomes, but also understanding the specific and separate contributions of both structural and functional connectivity to predicting individual L2 learning abilities.

To summarise the different choices of methods and measures used for the current dissertation, we were interested in exploring brain characteristics underlying the variability of individual L2 learning abilities using dMRI tractography to examine structural connectivity and resting-state fMRI functional connectivity to examine functional connectivity. Studying brain function and organisation requires a multimodal approach to understand how specialised regions interact; using these two methods enables us to investigate different aspects of connectivity and how well they relate to outcomes of interest. These methods, combined with a longitudinal study design and investigating multiple components of language, can inform us about the different ways the brain is wired to promote learning various aspects of language.

I.2. Language and the brain

Several decades of research using the previously-described methods have helped us establish which brain regions are critical for language processing, as well as how they are connected and function together. An overview of these language regions is necessary to understand studies of brain areas supporting language processing and learning.

I.2.1. Neuroanatomy of language

Classical studies of patients with brain lesions led to the description of two key brain regions that appear crucial to language: an area in the inferior frontal gyrus (IFG) of the left hemisphere involved in speech production, which has come to be known as Broca's area (Broca 1861), as well as an area of the left superior temporal gyrus (STG) involved in speech comprehension, known as Wernicke's area (Wernicke 1874). Following the early work on brain lesions which revealed that the brain can be divided into different functional regions, cytoarchitectonics further revealed that these regions can be divided based on their cellular architectures. These cytoarchitectonic regions were presumed to constitute functional units of the brain (Meynert 1867) and were later used to create cytoarchitectonic maps of the brain (Campbell 1905; Brodmann 1908). We now know that the language network actually comprises several other perisylvian regions and subregions in the frontal, temporal, and parietal lobes of each hemisphere that are implicated in language functional processes, beyond speech production and comprehension (Dejerine 1891a; Dejerine 1892; Geschwind 1970; Catani et al. 2005; Binder et al. 2009; Price 2010; Petrides 2014a), and that there is intra- and inter-hemispheric communication between these regions (Vigneau et al. 2011; Hinkley et al. 2016), as well as involvement of subcortical structures (Kotz et al. 2009) and the cerebellum (De Smet et al. 2013; Mariën and Borgatti 2018). Focusing on the role of the perisylvian cortical areas involved in language processing and the WM pathways connecting them, illustrated in Figure I.1, the following section will describe in more detail the anatomy and roles of the frontal, temporal and parietal regions in language.

The IFG has been known as an area of importance in language since the early work of Broca (1861) on patients with brain lesions. In the ventrolateral frontal region, three cytoarchitectonically distinct areas can be found: area 45 on the pars triangularis and area 44 on the pars opercularis in the IFG, and premotor area 6 (Petrides 2006; Petrides 2015). Although areas 45 and 44 are often investigated jointly as Broca's area or the IFG, we know that not only are they cytoarchitectonically distinct, but they also play different roles in language processing and have different anatomical connectivity profiles (Petrides and Pandya 1984; Petrides and Pandya 2009; Petrides 2015). In terms of functional contributions, area 45 is involved in higher order processes such as retrieving verbal information from memory (Klein et al. 1995; Petrides et al. 1995; Petrides and Pandya 2002; Heim et al. 2009) and semantic processing and comprehension (Dapretto and Bookheimer 1999; Gough et al. 2005; Hagoort 2005; Mainy et al. 2007), while area 44 is involved in articulatory aspects of speech production (Horwitz et al. 2003; Heim et al. 2009; Papoutsi et al. 2009; Church et al. 2011; Clos et al. 2013). Given its position between area 45 and ventral premotor area 6, which controls the orofacial musculature, area 44 has been proposed as an intermediary area between cognitive retrieval and articulation (Petrides 2014b). Other regions of the frontal lobe also contribute to language processing, such as area 8a in the middle frontal gyrus (MFG), which plays a role in regulating attention (Petrides 2006; Petersen and Posner 2012; Petrides 2015) and area 9/46v, which is implicated in monitoring the articulatory aspects of speech in working memory (Petrides 2000; Petrides 2006; Petrides 2015).

Two other perisylvian regions have long been known to be involved in language. Based on lesion studies and aphasia, Wernicke first proposed that the STG may be involved in auditory language comprehension (Wernicke 1874). More recent methods have helped to establish that the temporal lobe plays an important role in speech perception and comprehension, in particular the STG and middle temporal gyrus (MTG) (Price 2010; Friederici 2011). In addition, the inferior parietal lobule (IPL), with its proximity to the STG, was also thought by some to be a critical region for language (Marie 1906) based on studies of patients with aphasia, and was shown to play a significant role in reading and writing (Dejerine 1891a; Dejerine 1891b; Dejerine 1892). Though often investigated as a single region, the IPL is known to comprise two cytoarchitectonically distinct regions, the supramarginal gyrus (SMG) and the angular gyrus (AG), which in fact have different functional contributions in language processing (Petrides and Pandya 1984; Petrides and Pandya 2009). The SMG is involved in phonological processing and speech production (Price 2010; Oberhuber et al. 2016), while the AG is involved in verbal retrieval (Price 2010; Herbet et al. 2016; Linden et al. 2017) and reading (Horwitz et al. 1998; Seghier 2012).

Left-hemispheric dominance for language in the majority of the population is well established (Geschwind 1970; Geschwind and Galaburda 1985), which is why language studies are typically focused on the left hemisphere. However, it is also known that the homologues of these regions in the right hemisphere are involved in language processing. The most recognised role of the right hemisphere in language is for supra-segmental and abstract language processing (Bottini et al. 1994; Beauregard et al. 1997; Buchanan et al. 2000). Other work has shown the

right hemisphere may play a role in other aspects of language such as sentence and discourse processing (Gernsbacher and Kaschak 2003; Vigneau et al. 2011) and overall language ability including semantics, syntax and pragmatics, verbal fluency and comprehension ((Van Ettinger-Veenstra et al. 2012). Thus, it seems important that investigations of language processing consider bilateral perisylvian contributions.

Now that we have considered the roles of some of the individual language regions, we can focus on understanding how they communicate in order to function as a network. As previously mentioned, this is achieved through the WM pathways of the brain. Based on the connections between those key language regions, several pathways that are crucial to language processing can be identified. As previously mentioned, studies in the macaque monkey have demonstrated the existence of regions homologous to human language regions (Petrides and Pandya 2002; Petrides et al. 2005), thus shedding light on the anatomical connectivity within the language network in the human brain. The most well-known and well-studied WM language tract is the arcuate fasciculus (AF), connecting so-called Broca's area to Wernicke's area. In more anatomically precise terms, the AF runs dorsally in the brain and connects area 44 with the ventral portion of the posterior third of the STG and superior temporal sulcus (STS), and area 45 with the caudal STG and STS (Frey et al. 2008; Petrides and Pandya 2009; Petrides 2014b). There is frequent amalgamation of the AF with other WM tracts running dorsally, and the disproportionate focus on the AF tract has led to relative neglect of direct investigations into the roles of other dorsal pathways in language (see Dick and Tremblay 2012 and Tremblay and Dick 2016, for review). The main pathway for which this is an issue is the superior longitudinal

fasciculus (SLF), which connects frontal to parietal regions. This tract can be further subdivided into three branches, and branches II and III highlight the different connectivity profiles of area 45 and area 44 with the inferior parietal lobule (Petrides and Pandya 1984; Petrides and Pandya 2009). The second branch of the SLF, SLF II, links the AG in the IPL with ventrolateral frontal areas 45 and 8a, while the third branch, SLF III, connects the SMG in the IPL with ventrolateral frontal areas 44, 6 and 9/46v (Frey et al. 2008; Petrides and Pandya 2009; Petrides 2014b). Area 45 is also connected to the middle portion of the STG and STS via a WM pathway running ventrally through the extreme capsule, the extreme capsule fasciculus (ECF, Petrides and Pandya 1984; Petrides and Pandya 2009). Beyond evidence from tracer studies of homologous language regions in macaque monkeys, rsFC (Kelly et al. 2010) and dMRI tractography (Frey et al. 2008) studies support the existence of these WM connections in the human brain.

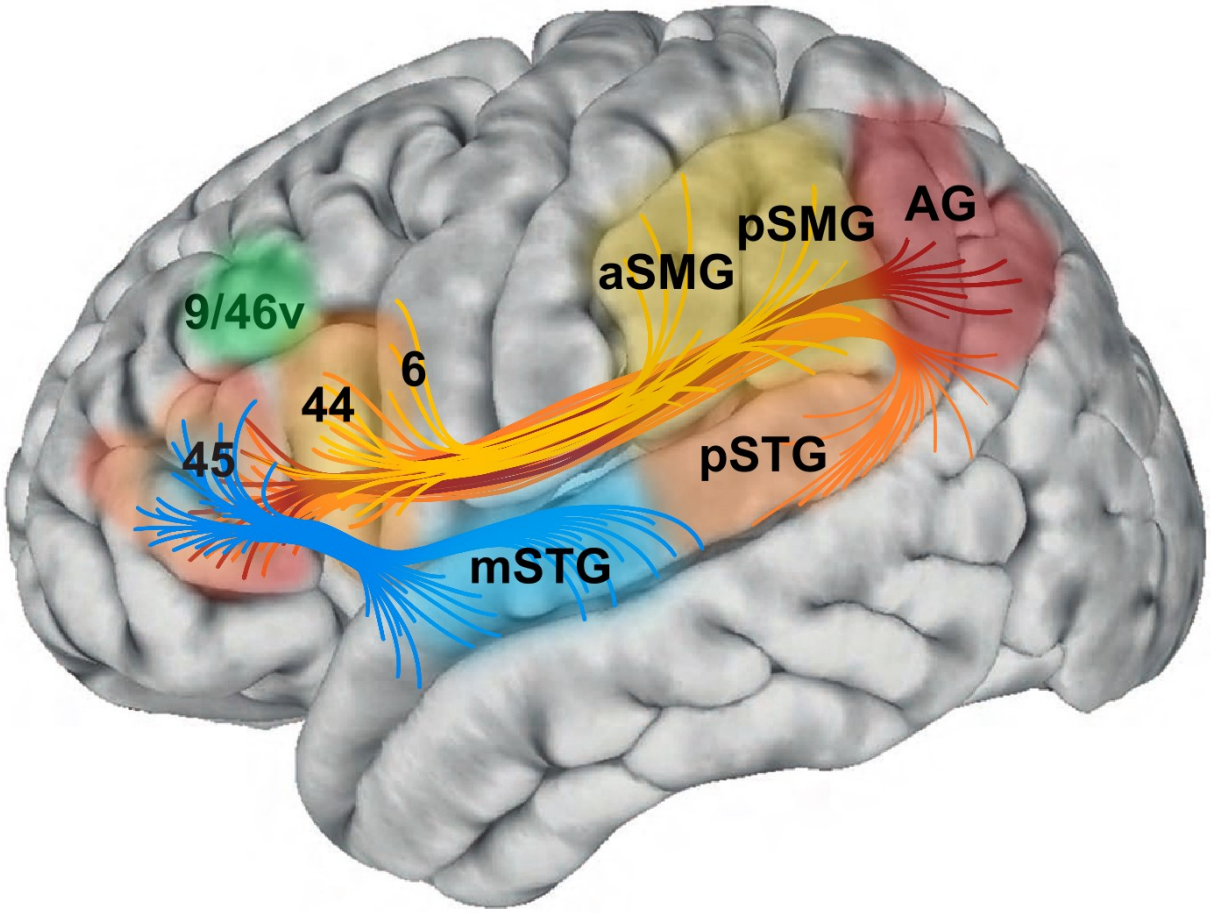

Figure I.1. Illustration of the main perisylvian cortical regions of the brain and their white matter connections in the left hemisphere. The different regions are: mSTG = middle superior temporal gyrus in blue, pSTG = posterior superior temporal gyrus in orange, aSMG = anterior supramarginal gyrus in yellow, pSMG = posterior supramarginal gyrus in yellow, AG = angular gyrus in red, 9/46v = area 9/46v in green, 45 = area 45 in blue-orange-red, 44 = area 44 yellow-orange and 6 = area 6 in yellow-orange. The different WM tracts are the extreme capsule fasciculus in blue, the arcuate fasciculus in orange, the second branch of the superior longitudinal fasciculus (SLF II) in red and the third branch of the SLF (SLF III) in yellow. Adapted from (Petrides 2014b).

I.2.2. Neurobiological frameworks of language

With knowledge of the functions of individual regions involved as well as the anatomical connections between those regions, models of language processing can be developed to understand how language relates to the brain. A brief overview of the key neurobiological frameworks will be provided here, as understanding how brain areas function together to permit the production and comprehension of language is also critical for understanding the factors involved in the acquisition of a new language. The earliest and most basic model, sometimes referred to as the Wernicke–Lichtheim–Geschwind model, involved only so-called Broca's and Wernicke's areas and the AF. According to this model, Broca's area represents the centre for speech planning and production, Wernicke's area represents the auditory centre, storing information about the sound of words and a third, conceptual region distributed throughout the brain stores information about word meanings (Geschwind 1970; Hux 2011; Tremblay and Dick 2016). While many more recent and elaborate models of the functional anatomy of language exist, one of the most well-known and widely-accepted models is the Dual-Stream model proposed by Hickok and Poeppel (2004; 2007). The basis of this model is that, after bilateral speech perception and early processing in the lateral STG and middle STS, further processing is split into two separate streams: a weakly left lateralised ventral stream and a strongly left-lateralised dorsal stream. The ventral stream, for mapping sound to meaning i.e., speech comprehension, projects towards other temporal areas including the posterior MTG and inferior temporal gyrus (Hickok and Poeppel 2004). In contrast, the dorsal stream maps sound to articulation and projects towards inferior parietal regions and frontal regions that include the posterior IFG and the anterior insula (Hickok and Poeppel 2004; Hickok and Poeppel

2007). Further investigation into the neuroanatomical basis of the ventral stream found that sentence comprehension was mediated by the left ECF, connecting the MTG to ventrolateral prefrontal regions (Saur et al. 2008). Sound-to-articulation, as measured by word vs pseudoword repetition, was found to be mediated by the left AF and the SLF (Saur et al. 2008). Thus, the ventral processing stream relies on the ECF connecting the temporal to frontal lobes to mediate speech comprehension, while the dorsal stream relies on the AF for fronto-temporal connections and on SLF II and III for fronto-parietal connections to mediate speech production (Weiller et al. 2016).

I.3. Second language learning and the brain

Learning a first language is a natural process that occurs easily during childhood in normal development. However, as already mentioned, learning a second language in adulthood occurs very differently. One reason for this is that it must be learnt in the context of the already existing L1 framework, which presumably affects the neural L2 learning processes as well as their neural representation (Hernandez 2016). Various factors have been shown to play a role in the variable outcomes of L2 learning in adulthood. Such factors include age of acquisition (Long 1990; Hakuta et al. 2003; Birdsong 2018), mode of acquisition (Freed et al. 2004) and motivation (Schmidt 2001; Masgoret and Gardner 2003), among others. In particular, age of acquisition is an important factor in L2 learning due to evidence of critical or sensitive periods that may constrain native-like language attainment past a certain age (Penfield and Roberts 1959; Birdsong 2018), usually thought to be around puberty (Lenneberg 1967; Muñoz and Singleton 2011). Since the studies presented in this dissertation focused on adult learners past

the hypothesised age of critical periods, detailed discussion of the critical period hypothesis is beyond the scope of this dissertation. In addition, individual variability in L2 learning abilities is a major factor that can be influenced by personal experience, differences in biology, cognitive capabilities and L1 background (van den Noort et al. 2006; Birdsong 2018). The interplay between these factors and L2 learning is complex. For example, different aspects of language are differentially affected by age of acquisition (such as phonology and grammar that are more difficult to learn as age advances). The L1 background also has an effect on L2 learning particularly with a later age of acquisition, since the L1 sound system is more engrained (Hernandez 2016), and cross-linguistic differences or similarities between the L1 and language being learned can facilitate or slow the learning process, especially during initial stages of acquisition (Cenoz 2001; Collins 2002; Vallerossa 2021). Disentangling the influence of these different factors is a large undertaking, but one definitive contributor to individual differences in L2 learning abilities is the brain (Biedroń 2015). Therefore, this section will give a brief overview of the main brain regions and networks implicated in L2 learning acquisition in adults, as well as gaps in knowledge left by existing studies.

I.3.1. Plastic changes relating to L2 learning

As complex cognitive functions, language and learning are undeniably rooted in the brain. Rather than looking at brain differences between individuals who have already learned a new language (i.e., bilinguals), and those who have only learned their native language (i.e., monolinguals), this dissertation seeks to examine the brain regions involved in the intermediate process that occurs in the early stages of L2 learning. A number of changes in the brain, i.e.,

neuroplasticity, occur as a result of L2 learning, whether at the start of learning a new language or after years of experience. These changes, both structural and functional, reveal the brain regions that support language learning. Thus, it is crucial to review some of the neuroplastic changes underlying L2 learning in order to improve hypotheses concerning predictors of L2 learning success.

Structural correlates

Investigations into the brain structures underlying second language acquisition have revealed important regions and networks, notably the IPL. Indeed, the grey matter density (GMD) of the left IPL was found to increase with L2 proficiency (Mechelli et al. 2004) and multilingual competence (measured by grades, Della Rosa et al. 2013), while increased GMD in the right IPL was found in individuals able to speak two or more non-native languages (Grogan et al. 2012). Similarly, individuals who were better able to pronounce newly heard foreign speech sounds had higher white matter density (WMD) bilaterally in the IPL (Golestani and Pallier 2007). Various regions within the temporal lobe have also been frequently implicated in L2 learning. For instance, increases in GMD of the left anterior temporal lobe (Stein et al. 2012) and in cortical thickness of the left STG (Mårtensson et al. 2012) were found after a few months of learning and correlated with proficiency in the L2.

Another key region underlying L2 learning is naturally the IFG. Increases in cortical thickness (Mårtensson et al. 2012) and GMD (Stein et al. 2012) of the left IFG have been observed as a result of L2 training. In addition, the right IFG has also been implicated, with increases in grey

matter volume occurring after several weeks of L2 learning (Hosoda et al. 2013). Changes to the white matter pathways have also been related to L2 acquisition. Increases to the microstructure of the SLF in the left and right hemispheres have been observed as early as 16 days after the start of learning (Mamiya et al. 2016) and as a result of bilingualism (Luk et al. 2011; Pliatsikas et al. 2015). Pathways of the right hemisphere are also implicated, with one study reporting FA increases of the dorsal pathway correlated with gain in L2 ability (Hosoda et al. 2013). Finally, the corpus callosum (CC), which connects the two hemispheres of the brain, also plays an important role in supporting L2 learning, as several studies report changes to the CC as a result of short-term learning (Schlegel et al. 2012) and life-long bilingualism (Luk et al. 2011; Pliatsikas et al. 2015). This evidence indicates that critical language regions in each hemisphere, as well as the connections between them, are implicated in L2 learning (Qi and Legault 2020).

Functional correlates

Some of the evidence from functional studies investigating the brain regions involved in acquiring a new language seems to converge with the structural findings just discussed. Post-learning increases in activation in the left IPL during task-based fMRI have been observed in relation to improved reading speed (Barbeau et al. 2017) and better tonal word learning (Yang et al. 2015). Using magnetoencephalography (MEG) to measure the response to learning new vocabulary also revealed learning effects in the left IPL (Cornelissen et al. 2004). In addition, the temporal and inferior frontal lobes have been functionally implicated in various aspects of L2 learning. Increased recruitment of the left STG and left IFG was associated with better learning

of non-native sounds (Golestani and Zatorre 2004), while increases in the right IFG were associated with learning Mandarin tones (Wang et al. 2003). Similarly, learning new words in an L2 has been linked with increased activation in the left posterior STG (Wong et al. 2007) and bilateral posterior MTG (Yang et al. 2015). Additional data from a meta-analysis of functional neuroimaging studies of L2 learning indicate involvement, among others, of the IPL, IFG and temporal regions in lexical and grammatical learning (Tagarelli et al. 2019). Studies have also shown that changes in functional connectivity occur with L2 acquisition, both within and between hemispheres. Connectivity between the left and right SMG was found to increase in a group of participants who learned new L2 vocabulary compared to non-learners, again highlighting the role of the IPL (Veroude et al. 2010). Findings also show that FC between the left and right STG increases after training in tone discrimination (Deng et al. 2018) and that the rsFC between left and right IFG increases is associated with successful L2 attainment after training (Qi et al. 2019). Taken together, these studies emphasise the role of interhemispheric interactions in L2 learning (Qi and Legault 2020). In addition, the rsFC between the left superior parietal lobule (SPL) and frontal areas seems to be important for L2 learning, with one study reporting reduced intrahemispheric rsFC between the left frontal operculum/anterior insula (LFO/AI) and the left SPL (Ventura-Campos et al. 2013) after training on a phoneme discrimination task, and another reporting increases in rsFC across hemispheres between the right IFG and left SPL relating to better L2 learning (Qi et al. 2019), though the contradictory patterns of change complicate interpretation. However, overall these findings add to the evidence that L2 learning is supported by a bilateral network that includes, among others, regions of the IFG, the IPL and the STG.

Global patterns of neural changes with L2 learning

Beyond simply identifying changes in and between specific brain regions of interest, evidence regarding the neural correlates of L2 learning can help us identify global patterns of change throughout the brain. In addition, investigating the neural changes related to L2 learning from the early stages of learning to later stages with more extensive L2 experience enables the building of a timeline of changes occurring in the adult brain with the acquisition of a new language. There are still few studies elucidating the general neural trends associated with L2 learning, but some evidence indicates that the L2 learning process mimics that of L1 acquisition in children (Galloway and Krashen 1980; Obler 1981). This involves a shift in laterality from the left to the right hemisphere, followed by a shift back to left hemisphere laterality (Qi and Legault 2020), with brain activation patterns becoming more similar to the L1 as proficiency increases (Green 2003; Sharwood Smith 2014). Thus, frontal, temporal and parietal regions of the right hemisphere seem to support the initial stages of L2 learning (Wang et al. 2003; Hosoda et al. 2013; Kepinska et al. 2018; Qi et al. 2019), followed by a shift to the left hemisphere (Hosoda et al. 2013; Xiang et al. 2015; Qi et al. 2019). This shift could support L2 proficiency and rely on better interhemispheric communication (Schlegel et al. 2012; Qi et al. 2019)). Elucidating these more global patterns of laterality shifts provides important context when interpreting neural patterns related to L2 learning and may represent a key step in understanding the L2 acquisition process in the adult brain.

I.3.2. Biomarkers of L2 learning

The previously discussed evidence about the main language regions of the brain and their roles and plastic changes during language acquisition allows us to formulate hypotheses about the patterns of brain organisation that could promote L2 learning success. Thus, we can discuss neural biomarkers or predictors of L2 learning. A biomarker has been defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes" (Biomarkers Definitions Working Group 2001). In the context of this dissertation, the characteristics are structural and functional brain connectivity, measured by dMRI and rs-fMRI as indicators of L2 learning ability. In addition, these methods enable us to study individual differences in L2 learning and further understand L2 learning variability (Li et al. 2014) by relating brain connectivity to individual L2 learning performance.

Structural biomarkers

Certain indices of brain structure have been shown to be predictive of specific L2 improvements. Intrinsic left auditory cortex WM anatomy, including WMD in Heschl's gyrus (Golestani et al. 2007), as well as WMD in the left IPL (Golestani et al. 2002), predict learning of foreign speech sounds. Left Heschl's gyrus is also implicated in learning pitch patterns resembling Mandarin tones, with larger GM and WM volumes predicting better learning (Wong et al. 2008). In terms of findings more relevant to the present dissertation, properties of WM tracts have also been shown to predict language learning. Properties of the right SLF have been linked to language learning outcomes, with one study showing that FA could be used as a

predictor of students' grades in a language class (Mamiya et al. 2016), and another showing that a larger initial FA was correlated with better Mandarin learning (Qi et al. 2015). Properties of the left AF have also been linked to better word learning ability (López-Barroso et al. 2013). And finally, language tracts of the left ventral stream, a combination of the extreme capsule fasciculus and inferior longitudinal fasciculus, have also been shown to predict perceptual ability in learning new words with tones similar to Mandarin (Wong et al. 2011). Taken together, these findings not only illustrate that specific anatomical characteristics are associated with better L2 learning abilities, but that connectivity between specific areas seems to prime the brain for L2 learning.

Functional biomarkers

The degree of functional activation of various language regions can also predict L2 learning success. Higher activation of the left posterior MTG and STS was found in more successful learners or auditorily-presented words (Mei et al. 2008), as well as higher activation of the bilateral STG and MTG in more successful learners of pitch patterns resembling Mandarin (Wong et al. 2007). Greater pre-training activation of the right IFG was related to better Mandarin L2 learning outcomes, measured by pre-training, in-scanner speech tone discrimination (Qi et al. 2019). Furthermore, patterns of functional brain organisation, in terms of connectivity and networks, have been shown to predict L2 learning as well. In a graph theory analysis of functional networks, more successful learners of auditory pitch patterns had increased global efficiency (i.e. efficient integration of information across the brain) compared to less successful learners who had better local efficiency (i.e. greater local interconnectivity,

Sheppard et al. 2012). This is consistent with other findings of functional connectivity between distant brain regions relating to better L2 learning. For instance, one study reported that the pre-training strength of rsFC between the left insula/frontal operculum and the left SPL predicted the ability to learn to discriminate foreign sounds (Ventura-Campos et al. 2013). Another study showed that individuals who were better able to learn novel words in a foreign language had stronger FC between the left supplementary motor area and the left precentral gyrus, as well as the left insula and the left rolandic operculum, compared to those who were less able to learn new words (Veroude et al. 2010). In addition, differential patterns of rsFC have been shown to relate to different aspects of L2 learning. The strength of pre-learning rsFC between the left anterior insula/frontal operculum and the left posterior STG was found to predict improvement in lexical retrieval during spontaneous speech, while pre-learning rsFC between the Visual Word Form Area and the left mid-superior temporal gyrus predicted improvement in reading speed (Chai et al. 2016). Though less clear than the anatomical evidence of structural biomarkers, these findings indicate that specific patterns of brain activation seem to facilitate more successful L2 learning.

I.4. Rationale and summary of studies

The following section outlines the current gaps in knowledge that remain in the L2 learning literature, particularly in relation to the study of biomarkers. Issues of both a methodological and conceptual nature remain, which this dissertation aims to address.

I.4.1. Issues with current L2 learning studies

Despite all the presented evidence on neural correlates and predictors of L2 learning, there is still much we do not know about individual variability in L2 acquisition, and more systematic and comprehensive investigations are required. One main issue concerns the lack of anatomical specificity. In terms of structural connectivity, in addition to the previously mentioned lack of anatomical dissociation between different components within the dorsal pathway (see Dick and Tremblay 2012 and Petrides 2014b, for in depth discussion of the issue), such a lack of separation of individual components is also present in investigations within the ventral stream (Wong et al. 2011) and even within a single tract, with several studies not separating SLF II and SLF III (Luk et al. 2011; Pliatsikas et al. 2015; Qi et al. 2015; Mamiya et al. 2016). Lack of anatomical precision is also apparent when studying individual language regions. The IFG or Broca's area is often studied as a single entity (Golestani and Zatorre 2004; Mårtensson et al. 2012; Stein et al. 2012; Qi et al. 2019) even though it comprises two distinct cytoarchitectonic regions with different functional roles, areas 44 and 45 (Petrides 2006). This type of concern may also be seen in studies implicating parietal regions, with many studies referring to the IPL rather than specifically the SMG or the AG (Golestani et al. 2002; Mechelli et al. 2004; Della Rosa et al. 2013). Furthermore, ample evidence indicates the involvement of the right hemisphere in language processing (Vigneau et al. 2011) and learning (Qi and Legault 2020), as well as bilateral involvement (Golestani and Pallier 2007; Wong et al. 2007; Yang et al. 2015) and interhemispheric communication (Veroude et al. 2010; Deng et al. 2018; Qi et al. 2019). However, specific investigations into the role of hemispheric interactions in L2 learning are limited. In addition, many studies of L2 learning examine or report only on a single aspect of L2

learning (e.g., pitch discrimination or word learning). Another issue is only looking for global structural correlates using Tract-Based Spatial Statistics (TBSS, a method for assessing measures of major WM pathways across the brain for a group of subjects, Smith et al. 2006), rather than specific pathways (Luk et al. 2011; Pliatsikas et al. 2015; Mamiya et al. 2016). Few current studies of L2 learning attempt to dissociate the connectivity of distinct language regions to relate the patterns of connectivity to improvement in specific, predicted aspects of L2 learning (but see Chai et al. 2016). More targeted, hypothesis-driven investigations of particular brain connections and their specific language involvement are needed to establish more fine-grained biomarkers underlying L2 learning success. Moreover, in addition to only investigating one aspect of language, many of the previously mentioned studies focus on perceptual aspects of L2 learning, such as learning foreign speech sounds, pitch and words presented in the auditory modality. Investigating the learning of various features of foreign speech production is also of interest. Finally, particularly in the case of functional studies of L2 learning, patterns of brain predictors or changes are often examined at the group level, i.e. “good” versus “poor” language learners (Wong et al. 2007; Mei et al. 2008; Sheppard et al. 2012), rather than at the individual level, and thus more work is required to establish individual biomarkers of L2 learning success.

Taken together, these issues indicate a need for more anatomically precise, comprehensive, and hypothesis-driven investigations of cerebral connectivity related to improvement in specific aspects of an L2 at the individual level. That is, specific relationships between connectivity of target brain regions and behavioural outcomes that are hypothesised to be related need to be established.

I.4.2. The present investigation

This section outlines the studies conducted for this dissertation. The overall aim of this dissertation was to improve understanding of the individual differences in L2 learning variability in terms of brain connectivity factors, while addressing the previously described issues. The first study explored structural connectivity biomarkers of L2 learning, while the second explored functional connectivity predictors of language learning in adults.

General methods

Whereas the two studies differed in terms of the type of connectivity explored and the specific methods utilised, as well as brain regions and behavioural measures examined, some methodology was common to both. Both studies were longitudinal, following the same participants undertaking a French learning course and with two testing time points: time 1 (t1) prior to the French learning course, and time 2 (t2) after conclusion of the course (~80 hours of language training). Behavioural measures were acquired at t1 and t2 to measure learning progress, and imaging data were acquired at t1 to determine individual pre-existing brain connectivity and at t2 to look at brain plasticity (although this second aspect is beyond the scope of this thesis). In order to establish biomarkers, the initial, intrinsic brain connectivity of each individual (at t1) was related to the L2 behavioural improvements between t1 and t2. Both studies were conducted using the same dataset of 18 participants who received about 80 hours of training in French from a course at McGill University. Within these participants were two subgroups, one whose L1 was English and the other whose L1 was Mandarin (but who also

spoke English). These groups were recruited in an effort to find the most homogenous groups possible, but also to enable the examination of language learning in individuals with different language backgrounds. Differences between the groups were examined but none were found, and thus both studies were conducted using one group including all 18 participants. Given the slightly different language backgrounds of the two groups, for ease of reading, regardless of language group, the language being trained, French, is referred to as the L2 throughout this dissertation.

Study 1 - Frontoparietal anatomical connectivity predicts second language learning success (Published in *Cerebral Cortex*, 2021)

This first study was designed to explore predictors of L2 learning success relating to brain structural connectivity. Due to the predominant focus on the role of the AF and fronto-temporal regions (Dick and Tremblay 2012; Tremblay and Dick 2016) as well as the known involvement of the IPL in L2 learning abilities (Grogan et al. 2012; Della Rosa et al. 2013), we decided to focus on connections between the parietal and frontal lobes, mediated by the SLF. Previous studies have implicated the SLF in bilingualism and L2 learning, but few, if any, separate the SLF from the AF, let alone separate the SLF II and SLF III branches from each other. Although both SLF II and SLF III are known to connect different regions of the IFG and the IPL, and thus can be presumed to contribute to different language-related functions, they have not yet been investigated in relation to specific L2 learning abilities. Their individual roles in language and its acquisition can be inferred based on the functional processes of the regions they connect. Indeed, SLF II connects area 45 in the IFG to the AG in the IPL, regions generally

implicated in retrieval of verbal and semantic information (Petrides et al. 1995; Petrides 2002; Heim et al. 2009; Linden et al. 2017). Conversely, SLF III connects areas 44 in the IFG to the SMG in the IPL, known to be involved in articulatory aspects of language and speech production (Heim et al. 2009; Price 2010; Petrides 2014a; Oberhuber et al. 2016). Therefore, we sought to differentiate the roles of SLF II and III in L2 learning by examining how their pre-learning properties are associated with specific, hypothesised improvements in L2. To this end, we used diffusion MRI tractography to reconstruct the tracts using precise dissection protocols and extracted a measure of WM microstructure (FA) in both left and right hemispheres. The FA measures were then related to specific language improvement measures based on the hypothesised functions of the WM tracts. Specifically, we expected SLF II pre-learning FA to relate to improvement in retrieving lexical items (measured as the number of novel words produced), and SLF III pre-learning FA to relate to improvement in articulatory aspects of language (measured by articulation rate).

Study 2 - Interhemispheric functional brain connectivity predicts new language learning success in adults (Published in *Cerebral Cortex*, 2022)

The second study aimed to investigate functional brain connectivity predictors of L2 learning success. In addition to the known roles of the left hemisphere in language processing (Vigneau et al. 2006; Price 2010), the right hemisphere has also been shown to play a significant role in language processing (Vigneau et al. 2011) as well as in L2 learning (Qi and Legault 2020). However, despite some evidence that communication between the hemispheres is important for language proficiency (Bartha-Doering et al. 2021a) and learning (Veroude et al. 2010; Qi et

al. 2019), few studies have investigated this directly. In addition, structural evidence implicating interhemispheric interactions in L2 learning and use focuses on the role of the corpus callosum itself (Coggins III et al. 2004; Felton et al. 2017), while functional evidence has focused on connectivity between specific language regions, such as the IFG (Berken et al. 2016; Qi et al. 2019). Building on this earlier work, the present study aimed to investigate the pre-learning interhemispheric connectivity of precise anatomical language regions in relation to the learning of specific aspects of a new language in adults. We chose several distinct language measures and related these measures to language regions reported to support these language functions based on the literature. We examined functional connectivity using resting-state fMRI to obtain resting-state functional connectivity (rsFC) measures; the chosen behavioural measures were sentence repetition, speech comprehension and reading speed. We hypothesised that the intrinsic interhemispheric connectivity of area 44 in the IFG and area 9/46v in the MFG would predict improvement in sentence repetition (Petrides 2002; Heim et al. 2009), that the interhemispheric rsFC of area 45 in the IFG and the middle STG would predict improvement in auditory speech comprehension (Friederici 2002; Heim et al. 2009) and finally that the initial rsFC between left and right AG (Seghier 2012; Barbeau et al. 2017) would predict improvement in reading speed.

Taken together, the results from both studies contribute to advancing our knowledge of the anatomical and functional brain connections implicated in successful L2 learning in adults. The next two sections will describe the investigations in further detail.

II. Study 1 - Frontoparietal anatomical connectivity predicts second language learning success

II.1. Preface

The overall aim of this first study was to focus on structural connectivity biomarkers of L2 learning success and determine whether intrinsic microstructural properties of WM tracts predict improvement in an aspect of language related to that tract. In particular, we decided to focus on the SLF, a somewhat neglected component of the language dorsal stream compared to the AF, within both the left and right hemispheres. We sought to determine whether more thorough efforts to distinguish anatomically the two branches of the SLF, SLF II and SLF III, by using existing knowledge from macaque tracer studies would enable us to also distinguish the language functions predicted by the WM properties of each tract. This is important to investigate in the context of this dissertation, because it helps us further understand whether pre-existing brain structure may play a role in influencing individual L2 learning abilities as well as demonstrating that different brain structural connections may differentially influence the learning of distinct language components.

II.2. Main manuscript

Kaija Sander, Elise B Barbeau, Xiaoqian Chai, Shanna Kousaie, Michael Petrides, Shari Baum, Denise Klein, Frontoparietal Anatomical Connectivity Predicts Second Language Learning Success, *Cerebral Cortex*, 2021; bhab367. Reproduced with permission from Oxford University Press.

Abstract

There is considerable individual variability in second language (L2) learning abilities in adulthood. The inferior parietal lobule, important in L2 learning success, is anatomically connected to language areas in the frontal lobe via the superior longitudinal fasciculus (SLF). The second and third branches of the SLF (SLF II and III) have not been examined separately in the context of language, yet they are known to have dissociable frontoparietal connections. Studying these pathways and their functional contributions to L2 learning is thus of great interest. Using diffusion MRI tractography, we investigated individuals undergoing language training to explore brain structural predictors of L2 learning success. We dissected SLF II and III using gold-standard anatomical definitions and related prelearning white matter integrity to language improvements corresponding with hypothesized tract functions. SLF II properties predicted improvement in lexical retrieval, while SLF III properties predicted improvement in articulation rate. Finer grained separation of these pathways enables better understanding of their distinct roles in language, which is essential for studying how anatomical connectivity relates to L2 learning abilities.

Introduction

Second language acquisition, specifically during adulthood, is a challenging process in comparison with native language acquisition (see Birdsong 2018 for review). It is known that there is considerable interindividual variability in second language (L2) learning abilities (Sparks et al. 1998; Golestani and Zatorre 2009; Jakoby et al. 2011), which has previously been shown

to relate to functional and structural brain connectivity within both hemispheres (López-Barroso et al. 2013; Ocklenburg et al. 2014; Qi et al. 2015; Chai et al. 2016). In addition to the classical posterior temporal and inferior frontal language processing areas, the inferior parietal lobule (IPL) has been investigated in relation to language learning and has even been described as a "location for multilingual talent" (Della Rosa et al. 2013). Specifically, L2 learning and proficiency have been related to the structure of the IPL in terms of gray matter (GM) density (Mechelli et al. 2004; Grogan et al. 2012), white matter (WM) density (Golestani and Pallier 2007), and functional involvement in learning-related changes (Cornelissen et al. 2004; Barbeau et al. 2017). The IPL comprises the supramarginal gyrus (SMG) and the angular gyrus (AG), which have specific and distinct WM anatomical connectivity with language regions in the frontal lobe (Petrides and Pandya 1984, 2009; Barbeau et al. 2020). However, to date, these specific connections have not been examined in relation to language learning and proficiency. It is, therefore, of great interest to study the different fronto-parietal pathways originating from the IPL to elucidate their particular functional contributions to specific aspects of individual L2 learning abilities.

The main WM tract that connects the IPL to frontal regions is the Superior Longitudinal Fasciculus (SLF). A recurring difficulty in the study of the SLF and language is that its frontoparietal trajectory is in close proximity to that of another major WM pathway involved in language, the Arcuate Fasciculus (AF), which connects ventrolateral frontal areas, or the classic Broca's area, to the posterior Superior Temporal Gyrus (pSTG), that is, the classic Wernicke's area. This anatomical proximity makes the separation of these pathways difficult in the human

brain using available methods, and given the focus on the AF in the literature because it connects the classical language areas, these pathways are frequently amalgamated. Indeed, many studies refer to this WM system as the AF/SLF (Dick and Tremblay 2012). This has led to a relative neglect of the study of the function of the SLF (Dick and Tremblay 2012; Gierhan 2013; Tremblay and Dick 2016), and although previous work has already anatomically distinguished the AF from the SLF in the human brain (Makris et al. 2005; Frey et al. 2008; Thiebaut de Schotten et al. 2012; Kamali et al. 2014; Barbeau et al. 2020), their anatomical and functional descriptions remain inconsistent between studies. Issues related to the separation of the tracts come mainly from the limitations of the technique used, diffusion MRI (dMRI), with which the main direction of major pathways can easily be demonstrated, but not the precise origin and termination of the tracts (Martino et al. 2011; Campbell and Pike 2014); in addition, determining whether connections are monosynaptic (i.e., direct) or polysynaptic is impossible. Thus, the gold standard remains the use of anatomical tracers in the macaque monkey, allowing the precise axonal origin, course, and terminations of tracts to be established. In the context of language, invasive studies in monkey models remain relevant because the existence of cytoarchitectonically homologous areas to the human language areas have been demonstrated (Petrides and Pandya 2002; Petrides et al. 2005; Petrides 2014). Thus, a priori knowledge of exact anatomical connectivity in nonhuman primate brains can inform in vivo studies in the human brain using dMRI (Campbell and Pike 2014; Schilling et al. 2020). The anatomical studies in macaque monkeys have provided precise connectivity information about cortical areas that, in the left hemisphere of the human brain, are known to be involved in language processes. Such approaches have allowed investigators to establish that not only do

frontal areas have distinct connections to posterior temporal areas through the AF and to the IPL via the SLF, but also that the SLF itself can be divided into three separate branches (Petrides and Pandya 1984). In these autoradiographic studies in monkeys, it has been shown that a specific branch of the SLF, that is, SLF II, connects the caudal IPL, homologue of the AG in the human brain, to ventrolateral frontal area 45 and area 8a which plays a role in regulating attention (Petrides and Pandya 1984; Petrides and Pandya 2006; Petrides 2015). In contrast, another branch of the SLF, that is, SLF III, originates from the rostral IPL, homologue of the SMG, and links it with area 44 (pars opercularis), ventral orofacial premotor area 6, which controls the orofacial musculature, and area 9/46v, which is involved in the articulatory loop of working memory (Petrides and Pandya 1984; Petrides and Pandya 2006; Petrides and Pandya 2009; Petrides 2014; Petrides 2015). Both tracts of interest in the present investigation are considered part of the dorsal stream within the framework of Hickok and Poeppel (2004). We have examined the involvement of SLF II (from the AG) and SLF III (from the SMG) in language processing. Previous studies in human subjects had separated SLF II from SLF III using dMRI (Makris et al. 2005; Galantucci et al. 2011; Kamali et al. 2014; Wang et al. 2016; Barbeau et al. 2020; Schurr et al. 2020) and resting state functional connectivity (Kelly et al. 2010; Margulies and Petrides 2013; Jakobsen et al. 2016), but the definitions of SLF II and III across studies have not always been consistent with each other. Thus, there remains much uncertainty surrounding the anatomy and functional role of these WM pathways in language (Makris et al. 2005; Kellmeyer et al. 2013; Nakajima et al. 2020).

Nonetheless, a few studies have suggested differential roles for these pathways in language. Involvement of SLF III in the articulatory aspects of language has previously been suggested (Kellmeyer et al. 2013; Duffau et al. 2014; Nakajima et al. 2020). Note that SLF III links the orofacial portion of premotor area 6 and area 44 (Broca's area) with the SMG, namely areas implicated in speech production and articulatory planning (Heim et al. 2009; Papoutsi et al. 2009; Price 2010; Bouchard et al. 2013; Oberhuber et al. 2016). In contrast, the role of SLF II is less clear, but its involvement in language seems evident based on its connections to area 45 of the IFG, and the fact that the AG is also thought to play an important role in language processing. It has been suggested that SLF II may be implicated in functional aspects, such as verbal working memory (Nakajima et al. 2020), semantic retrieval (Madhavan et al. 2014), and action naming (Akinina et al. 2019). This proposed role for SLF II in retrieval is consistent with proposals relating to functional contributions of the brain regions it connects. Indeed, both area 45 (Klein et al. 1995; Petrides et al. 1995; Petrides 2002; Heim et al. 2009) and the AG (Seghier 2012; Herbet et al. 2016; Linden et al. 2017) have been shown to be involved in the retrieval of information from memory. Based on this evidence, in the context of L2 learning, we hypothesize that SLF II facilitates retrieval of vocabulary from memory, but SLF III mediates planning and the articulatory aspects of speech in the new language. Thus, distinguishing SLF II and III from each other may allow us to determine their differential roles in language and how these distinct fasciculi relate to individual L2 learning abilities.

In the present study, we sought to differentiate the roles of SLF II and SLF III in L2 learning by investigating how structural connectivity to the AG part of the IPL via SLF II and the SMG part

via SLF III is associated with specific improvements in aspects of L2 that are related to the hypothesized functions of these WM tracts. One of the strengths of the study is the validity of our SLF II and III dissections, which are based on anatomical definitions from macaque tracer studies and comparative cytoarchitectonic analyses of the origins of the pathways (Petrides and Pandya 1984; Petrides and Pandya 2002), thus enabling accurate examination of their functional distinctions related to second language acquisition. Based on theorized involvement of SLF II in lexical retrieval and of SLF III in articulatory aspects of language, we focus on improvements in L2 vocabulary and articulation rate, respectively. We hypothesized that measures of WM properties of SLF II would be related to vocabulary acquisition, while SLF III WM properties would be related to improvements in articulation rate.

Methods

Participants

Eighteen participants (mean age 20.8 ± 3.9 years, 12 females) were recruited from a French language learning course. All participants were right-handed and had normal or corrected-to-normal vision, and reported no hearing impairments, history of traumatic brain injury, neurological disorders, or conditions incompatible with MRI scanning. Individuals with advanced musical training were excluded because of the known link between musical training and language ability (see Milovanov and Tervaniemi 2011 and Jäncke 2012 for review). Ten participants out of the 18 had American English as their native (L1) language (English group) and eight were native Mandarin speakers (Mandarin group) with English as their L2.

Recruitment was focused on speakers of these languages because they constituted the largest, most homogeneous groups of eligible participants. Individuals with high proficiency in languages other than English or Mandarin were excluded. The groups were matched on working memory and general intelligence (Table 1), as measured by the Digit Span, Letter-Number Sequencing, and Matrix Reasoning subtests of the WAIS-IV (Wechsler Adult Intelligence Scale; Wechsler 2008). No group differences in behavioral measures in English or French or in WM integrity measures were found pre- or postlanguage training and, therefore, we treated the participants as a single group for all analyses. All participants were students at McGill University, studying in English, and were considered beginner learners of French at the start of the study, which was approved by the Research Ethics Board of the Montreal Neurological Institute (MNI); the participants gave informed written consent.

Table 1. Mean ± SD of the WAIS-IV scores on various subtests for the English and Mandarin groups

	English L1	**Mandarin L1**	***t* statistic**	***P*-value**
Digit Span: Forward (/16)	11.7 ± 1.70	10.25 ± 1.91	1.70	0.108
Digit Span: Backward (/16)	8.6 ± 2.01	9.4 ± 2.07	0.83	0.420
Digit Span: Sequencing (/16)	8.3 ± 1.06	8.1 ± 2.30	0.25	0.809
Letter-Number Sequencing (/30	20.1 ± 1.3	19.8 ± 1.3	0.49	0.633
Matrix Reasoning (/26)	22.5 ± 1.12	22 ± 1.58	0.79	0.443

French Learning Course

The French learning course was a tertiary-level course for beginners offered by the McGill French Language Centre. Participants received approximately 80 h of training over one or two semesters, focusing on various aspects of language, such as grammar, writing, comprehension, and discussion of both audio and visual documents to develop their competency in multiple domains.

Language Tasks

The participants' language skills in French and English were assessed at the start (Time 1) and after completion of the French learning course (Time 2). Lexical retrieval and articulation rate were assessed quantitatively from a sample of spontaneous free speech using methods similar to Berken et al. (2015) and Chai et al. (2016). Participants were asked to describe two pictures of household scenes for 2 min using the "Cookie Theft picture" from the Boston Diagnostic Aphasia Examination (Goodglass et al. 2001) and the "Divided Attention picture" from the Kentucky Aphasia Test (Marshall and Wright 2007), in English and in French, respectively. The same pictures were used for all participants in each language and at each time-point (i.e., the "Cookie Theft picture" in English at Times 1 and 2 and the "Divided Attention picture" in French at Times 1 and 2) to control for potential variations in difficulty across the pictures. The same picture was used at Time 1 and Time 2 in order to be able to use the English version as a control, as no improvement was expected in English. The total number of correct and unique words (i.e., nouns, verbs, adjectives, prepositions, and determiners) was calculated as an index

of lexical retrieval (Chai et al. 2016). The mean number of syllables per second was also calculated and used as an index of articulation rate. We chose to focus on articulation rate rather than pronunciation or accent to examine articulatory aspects of language because accent has previously been linked to the basal ganglia (Berken et al. 2016). Both measures were extracted in French and English at Time 1 and Time 2, and the difference between the two time points was used as a measure of improvement in lexical retrieval and articulation rate.

Imaging Acquisition

Imaging data were acquired on a Siemens 3 Tesla MAGNETOM Prisma scanner at the McConnell Brain Imaging Centre at the MNI. Diffusion-weighted MRI data were acquired using a multiband EPI sequence (TR = 3000 ms; TE = 71.0 ms; 81 slices; b-values = 300, 1000, 2000 s/mm2; 108 gradient directions; voxel size = 2 mm3). High-resolution T1-weighted images were acquired using an MPRAGE sequence (TR = 2300 ms; TE = 2.96 ms; flip angle = 9°; 192 slices; voxel size = 1 mm3). Images were acquired at Time 1 and Time 2, but given the focus of this study on neuroanatomical predictors of language learning, only the Time 1 results are of relevance here.

Imaging Analysis

TractoFlow and Processing

Both the T1 and diffusion-weighted images (DWIs) were preprocessed using the TractoFlow pipeline (Di Tommaso et al. 2017; Kurtzer et al. 2017; Theaud et al. 2020).

Table 2. Mean ± SD (range) of the number of correct words produced (lexical retrieval) and syllables per second (articulation rate) before (Time 1) and after (Time 2) learning

	Lexical retrieval		**Articulation rate**	
	French	**English**	**French**	**English**
Time 1	30.5 ± 11 (18–55)	106.61 ± 45 (39–208)	0.76 ± 0.2 (0.54–1.32)	2.73 ± 0.64 (1.87–4.01)
Time 2	45.0 ± 11 (28–66)	105.72 ± 39 (45–164)	0.92 ± 0.22 (0.58–1.27)	2.70 ± 0.64 (1.56–2.84)

Table 3 Mean ± SD of FA for SLF II and SLF III in the left and right hemispheres

	Left FA	**Right FA**
SLF II	0.392 ± 0.03	0.405 ± 0.029
SLF III	0.415 ± 0.029	0.4124 ± 0.025

Diffusion-weighted images

The pipeline includes 14 steps for DWI processing and extracts both diffusion tensor imaging (DTI) metrics and fiber orientation distribution function (fODF) metrics. The main steps included denoising using the dwidenoise tool from MRtrix3 (Tournier et al. 2019), correction of deformation induced by the magnetic field susceptibility artifacts and eddy-currents as well as

brain extraction using the FSL package (Smith 2002; Jenkinson et al. 2012), N4 bias correction, cropping, normalization, and resampling before extracting the DTI and fODF metrics was applied (Garyfallidis et al. 2014). The number of shells specified to compute the DTI metrics was "01000," and "0 1000 2000" for the fODF shells.

T1-weighted images

The processing for the T1-weighted images in the pipeline consists of 8 steps, including denoising (Garyfallidis et al. 2014), N4 bias correction, brain mask extraction (Avants et al. 2008), registration of the T1 image to the DWI space (Avants et al. 2008), and tissue segmentation (Jenkinson et al. 2012) to compute the tracking maps.

Tractography

Whole-brain tractograms were generated using anatomically constrained particle-filtering probabilistic tractography (Girard et al. 2014; Barbeau et al. 2020; Theaud et al. 2020) and seeding from the WM/GM interface with 10 seeds per voxel and other parameters left as default. Finally, streamlines that were found to make a 300-degree loop onto themselves were removed (Barbeau et al. 2020).

SLF II and SLF III Tract Dissections

In order to implement the dissection protocol proposed by Barbeau et al. (2020), we first transformed the whole-brain tractograms into MNI space by using SyN ANTS (Avants et al.

2008) between the T1 image and the MNI 152 symmetric template and applying the transformation to the tractogram (Greene et al. 2018). Tract reconstructions were carried out manually using Trackvis (Wang et al. 2007) by creating Regions of Interest (ROIs) overlaid on individual normalized anatomical images in order to locate accurately the gyri and sulci for each participant, using coordinates and landmarks from Barbeau et al. (2020).

A first common inclusion ROI was created in the frontal lobe containing pars triangularis (area 45), pars opercularis (area 44), ventral premotor area 6 that controls the orofacial musculature, and areas 8a and 9/46 (single sphere, 30-mm radius centered at MNI coordinates x = −53, y = 27, z = 20 for the left hemisphere and at x = 49, y = 27, z = 20 for the right hemisphere). For SLF II, a second inclusion ROI was created in the AG (sphere, 20-mm radius centered at MNI x = −41, y = −68, z = 38 in the left hemisphere and x = 41, y = −65, z = 38 in the right hemisphere). The “either end” option was selected for both those ROIs to include fibers originating and terminating within those regions. Another inclusion ROI was drawn in the coronal view of the FA-color map, immediately under the central sulcus, to capture only fibers that are part of the frontoparietal WM.

For SLF III, an inclusion ROI was created in the SMG (sphere, 20-mm radius centered at MNI coordinates x = −55, y = −42, z = 36 for the left hemisphere and x = 55, y = −39, z = 37 for the right hemisphere), with the lower end of the sphere placed at the descending posterior ramus of the lateral fissure which separates the posterior end of the temporal lobe from the adjacent SMG of the parietal cortex. This approach ensured that no fibers originating in the nearby

posterior temporal gyrus were included. The AG sphere used for the reconstruction of SLF II was an exclusion ROI for SLF III so that only fibers originating from the SMG were included. Following Barbeau et al. (2020), the size of the spheres used was determined based on the size of the target area to ensure all the WM was included, focusing on distinguishing connectivity within the IPL.

To account for the individual variability that remains after normalization to MNI space, especially in the IPL, the SMG and AG ROI spheres had to be adjusted to fit individual anatomical landmarks (sulci and gyri). In addition, remaining streamlines clearly not belonging to the tracts of interest were removed with additional exclusion ROIs on a case-by-case basis.

After the tract dissections were completed, we extracted a measure of WM integrity, Fractional Anisotropy (FA), for SLF II and SLF III in both hemispheres for all participants, that is, an MRI measure of the diffusion of water molecules in the brain. If their diffusion is constrained by obstacles, such as myelinated WM fibers, it is expected to be anisotropic. We chose to focus on FA because of its widespread use as an index of WM microstructure, as well as the previous links between FA values and L2 learning success (Wong et al. 2011; Qi et al. 2015).

Statistical Methods

Paired t-tests were conducted to compare performance across Time 1 and Time 2 for each behavioral measure. We tested the hypothesized relationships between WM integrity (FA values) of SLF II and SLF III at Time 1 and behavioral improvement (Time 2–Time 1) using

directed Pearson correlations based on specific hypotheses. Specifically, we tested the SLF II FA values in relation to L2 improvement in lexical retrieval and SLF III FA values in relation to improvement in L2 articulation rate. Differences in correlation coefficients between groups were tested using Fisher r-to-z transformations.

Results

Behavioral Results

As expected, participants showed no difference in English across timepoints for lexical retrieval ($t(17) = 0.21$, $P = 0.8$) or articulation rate ($t(17) = 0.39$, $P = 0.7$, as shown in Table 2). However, participants improved significantly on the trained language, French, between Time 1 and Time 2 for both behavioral measures of interest (Table 2). For L2 (French), lexical retrieval scores (number of correct unique words) increased significantly ($t(17) = 5.9$, $P < 0.0001$) between Time 1 and Time 2. Articulation rate (syllables per second) also increased significantly ($t(17) = 4.2$, $P < 0.001$) at Time 2 compared with Time 1.

Tract Dissections

Both the SLF II and SLF III were successfully reconstructed in both hemispheres for all participants (see Fig. 1). Dissections were considered successful when the fibers coursed toward the frontal lobe originating specifically from the AG for SLF II, and from the SMG for SLF III, with SLF II coursing more medially and SLF III more laterally, as per Barbeau et al. (2020) and tracer studies in monkeys (Petrides and Pandya 1984). Measures of WM integrity were extracted for

SLF II (left mean FA = 0.392 ± 0.03, right mean FA = 0.405 ± 0.029, Table 3) and for SLF III (left mean FA = 0.415 ± 0.029, right mean FA = 0.4124 ± 0.025, Table 3), as well as for the whole brain (mean whole brain FA = 0.398 ± 0.018). There was substantial variability in lateralization between participants. For SLF II, six participants had greater FA in the left hemisphere. For SLF III, 11 participants had greater FA in the left hemisphere.

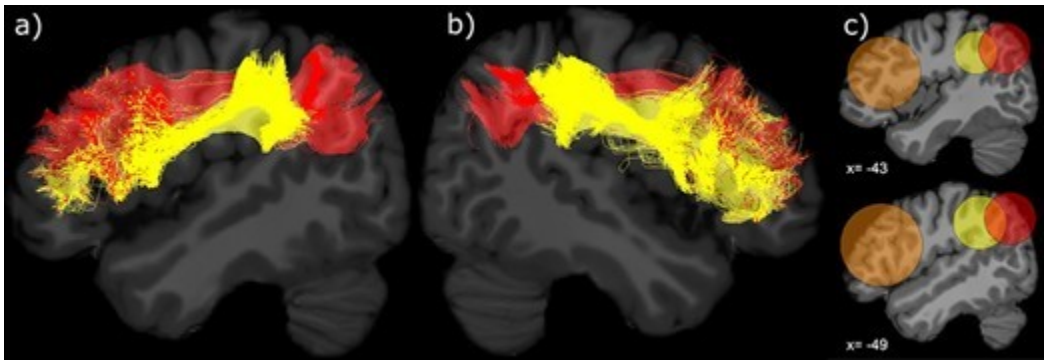

Figure 1. Example of the SLF II (red) and the SLF III (yellow) dissections in one participant. (*a*) Left hemisphere. (*b*) Right hemisphere. (*c*) Illustrations of the frontal (orange), supramarginal (SMG, yellow), and angular (AG, red) ROI spheres in two different sagittal sections. SMG and AG appear to overlap but are either inclusion or exclusion ROIs depending on the tract of interest. ROIs appear to extend beyond the brain to ensure that fibers terminating in the WM are included, but no fibers are present outside the brain and therefore, not included.

Time 1 SLF II FA and Vocabulary Change after Learning

To investigate the hypothesis that SLF II is involved in lexical retrieval, we conducted correlation analyses between the FA values for SLF II and lexical retrieval improvement based on training. We were specifically interested in how SLF II WM integrity in the left hemisphere related to lexical retrieval improvement after learning. FA values of the left SLF II at Time 1 correlated

positively with improvement in lexical retrieval (Time 2–Time 1) in French (see Fig. 2a, $r = 0.545$, $P = 0.019$), which indicates that individuals with higher initial FA improved more in the number of unique words produced after French training. FA of the right SLF II was not correlated with improvement in lexical retrieval ($r = 0.023$, $P = 0.9$). Furthermore, articulation rate was not correlated with FA in this tract in either hemisphere ($r = 0.229$, $P = 0.3$ for the left and $r = 0.157$, $P = 0.5$ for the right), suggesting that the link between the initial FA of SLF II and behavioral change is specific to the left hemisphere and related to lexical retrieval improvement. In addition, Fisher r-to-z transformation showed that the correlation coefficients between the English L1 and Mandarin L1 groups did not differ ($z = -0.36$, $P = 0.7$) and between the male and female participants did not differ either ($z = 1.41$, $P = 0.15$), and whole brain FA did not predict improvement in lexical retrieval ($r = 0.240$, $P = 0.3$).

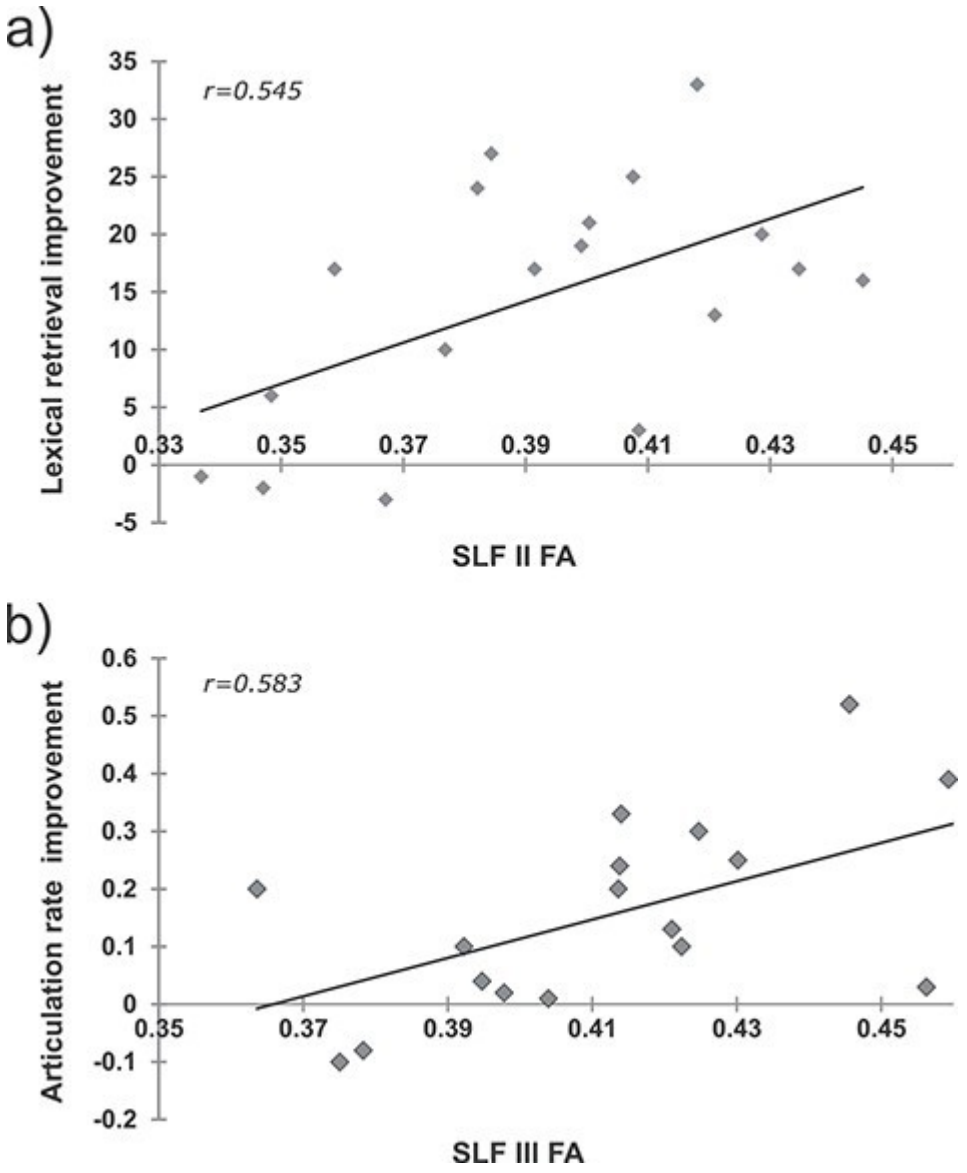

Figure 2. Relationship between behavioral improvement and prelearning FA values of the left hemisphere. (*a*) Improvement in lexical retrieval (number of words) plotted against the left SLF II FA. (*b*) Improvement in articulation rate (syllables/s) plotted against the left SLF III FA.

To investigate the hypothesis that SLF III is involved in articulation, we conducted correlation analyses between the FA values for SLF III at Time 1 and improvement in articulation rate after training. We were specifically interested in how SLF III WM properties in the left hemisphere related to change in articulation rate. Left SLF III FA values at Time 1 were positively correlated with improvement in articulation rate (Time 2–Time 1) (see Fig. 2b, $r = 0.583$, $P = 0.011$), which indicates that participants who had a higher initial FA showed more improvement in articulation rate after learning. FA of the right SLF III was not correlated with change in articulation rate ($r = 0.219$, $P = 0.3$). Lexical retrieval change was not correlated with FA of this tract in either hemisphere ($r = 0.337$, $P = 0.1$ for the left and $r = 0.077$, $P = 0.7$). This indicates that the link between the initial WM properties of SLF III and behavioral improvement is specific to the left hemisphere and to articulation rate improvement. In addition, Fisher r-to-z transformation showed that the correlation coefficients between the English L1 and Mandarin L1 groups did not differ ($z = 0.12$, $P = 0.9$) and between the male and female participants did not differ either ($z = 0.12$, $P = 0.9$), and whole brain FA did not predict improvement in articulation rate ($r = 0.367$, $P = 0.1$).

Discussion

The aim of this study was to examine the specific roles of SLF II and SLF III in second language (L2) learning by using precise anatomical tractography to examine their respective functional contributions to L2 learning success. We examined intrinsic structural connectivity from the IPL (SMG and AG) to the frontal language regions via the SLF II and SLF III pathways to establish anatomical predictors of L2 learning success following language training. A dissociable pattern

of correlations between WM integrity measures of the two pathways and their hypothesized involvement in language was observed. Pretraining left SLF II FA predicted improvement in lexical retrieval specifically, while pretraining left SLF III FA was only related to improvement in articulation rate. Thus, as a result of the anatomical separation of the SLF II and III, we provide empirical support for the hypothesized respective roles of these two separate branches of the left SLF in L2 learning.

The issue of separating the SLF II and III was of particular importance for this study in the context of L2 learning, as the IPL has been shown to be involved in L2 acquisition. Thus, the anatomical projections of the IPL to the language areas of the ventrolateral prefrontal cortex are relevant. Several studies have shown that the IPL is a critical brain region for various aspects of L2 proficiency and learning. Mechelli et al. (2004) reported that GM density was higher in the left IPL of more proficient bilinguals. Increased GM density of the IPL has also been observed in multilingual individuals (Grogan et al. 2012), in bilinguals with higher measures of multilingual competence (Della Rosa et al. 2013), and in studies of speech imitation aptitude (Reiterer et al. 2011). Furthermore, higher WM density of the IPL has been related to better pronunciation of foreign sounds (Golestani and Pallier 2007). Increased activation of the left IPL in fMRI studies has also been associated with L2 learning in relation to reading speed (Barbeau et al. 2017) and tone discrimination (Yang et al. 2015). In terms of frontoparietal connectivity and L2 learning, Yang et al. (2015) reported that better communication between the IPL and frontal cortex leads to more successful lexical processing of the tonal information in novel words in Mandarin. Connections between frontal and parietal areas have also been shown to relate to language

analytical abilities, a component of language aptitude (Kepinska et al. 2017). In addition, subnetworks of WM connecting frontal areas to the IPL (SMG and AG) have been found to be more strongly connected in bilinguals than monolinguals (García-Pentón et al. 2014). Thus, the role of the IPL in L2 learning and individual aptitude is well supported, as well as the importance of a frontoparietal network of connectivity.

One of the strengths of the present study is the use of a priori anatomical knowledge to define SLF II and SLF III using dMRI tractography (Barbeau et al. 2020). Inconsistent definitions of pathways have been particularly problematic in the context of language research (see Dick and Tremblay 2012 for review). Here, we based our definitions of SLF II and III on autoradiographic tracer studies, which are considered the gold standard for establishing anatomical connectivity in the brain, because they allow the establishment of the precise origin, trajectory, and termination of axons. In addition, knowledge of these WM tracts coming from macaque tracer studies is supported by evidence of corresponding resting-state functional connectivity in the human brain (Kelly et al. 2010; Margulies and Petrides 2013; Jakobsen et al. 2016). Comparable parallels between human and monkey brains have been drawn in relation to the mirror neuron system, which is found in the monkey homologue of area 44 and human area 44 and has been linked to speech processing (Rizzolatti and Arbib 1998; Corballis 2010); such studies support the relevance of nonhuman primate models to further our understanding of the anatomy of language in the human brain.

Using improved reconstructions of pathways, we examined the roles of the SMG (area 40) and the AG (area 39) and their respective frontal connections in order to disentangle their possible functional contributions. In particular, we were able to demonstrate a relationship between the FA values in SLF II and improvement in lexical retrieval (i.e., the number of new correct and unique words produced) during second language learning, consistent with the hypothesized role of this tract in language processing. Indeed, area 45 has been shown to be involved in the controlled selective retrieval of information (Petrides 2002), notably in the left hemisphere for verbal information (Klein et al. 1995; Petrides et al. 1995; Heim et al. 2009), while area 8a is involved in regulating attention (Petersen and Posner 2012; Petrides 2015). Several studies have highlighted the involvement of the AG in aspects of verbal retrieval (Price 2010; Seghier 2012; Herbet et al. 2016; Linden et al. 2017), as well as semantic processing (Binder et al. 2009; Van Ettinger-Veenstra et al. 2016). Moreover, the few studies referring to SLF II in the context of language appear to support the role of this tract in retrieval of verbal and semantic information (Madhavan et al. 2014; Akinina et al. 2019; Nakajima et al. 2020). Taken together, our finding that SLF II structure is predictive of the ability to retrieve new L2 vocabulary is consistent with previous research and suggests a potential role for the SLF II in facilitating improvements in L2 lexical learning.

Similarly, the association between the FA of SLF III and improvement in articulation rate is consistent with the literature (Kellmeyer et al. 2013; Duffau et al. 2014; Nakajima et al. 2020). The orofacial portion of area 6 in the ventrolateral precentral gyrus is essential for articulation (Bouchard et al. 2013). Area 44 has been proposed as an intermediary area between cognitive

retrieval and articulation (Petrides 2014), given its position between area 45 and the ventral premotor system, and has been shown to be involved in various aspects of speech production, such as phonological processing (Heim et al. 2008; Heim et al. 2009; Church et al. 2011; Clos et al. 2013), articulatory planning (Papoutsi et al. 2009; Price 2010), and other motor aspects of language (Horwitz et al. 2003; Nakajima et al. 2020). Area 9/46v is involved in working memory and enabling high-level planning and behavioral organization (Petrides 2015). There is also evidence that the SMG is involved in phonological processing (Oberhuber et al. 2016) and speech output (Price 2010; Oberhuber et al. 2016), particularly when speech production is made more difficult, which could include production in a second language, as well as selecting phonological information for language production (Corina et al. 1999). By connecting relevant brain regions, SLF III could enable speech production by facilitating the retrieval of phonological information and establishing motor articulatory plans (Rodríguez-Fornells et al. 2009); thus, better integrity of the SLF III tract could promote improvement in speed of speech output, consistent with what has been shown in the present study.

Interestingly, we did not find any group differences between the English monolingual and the Mandarin-English bilingual participants, which could indicate that these predictors of L2 success are present in individuals regardless of language background. However, in order to draw broader conclusions, the current results need replication with a larger sample and particularly in a sample undergoing longer term language training, as well as in participants with other language backgrounds.

Conclusion

Examining structural connectivity is crucial to understanding the functions of a given brain region, because knowing the other brain areas it specifically and directly interacts with informs us about the roles of the ROI. Thus, being anatomically precise when examining WM connections is relevant for elucidating functional differentiation between brain regions. In the present study, we report that the properties of the left SLF II support learning novel vocabulary in an L2, while the left SLF III supports articulation rate in the L2. This functional dissociation is in line with the previously suggested roles for SLF II and SLF III in language (Nakajima et al. 2020). Anatomical separation of SLF II and SLF III with tractography has rarely been demonstrated, and functional dissociation of these tracts in language learning had not been demonstrated before. The anatomical tract dissections in the present study allowed higher specificity in examining the functional contributions of the SLF II and SLF III and enabled us to demonstrate a functional dissociation between these branches of the SLF. In addition, these findings suggest that individual differences in L2 learning abilities can be explained by variations in intrinsic anatomical connectivity between specific language regions of the brain. Overall, the results reported here add to our understanding of the language networks that support L2 learning and its neuroanatomical predictors.

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III. Study 2 - Interhemispheric functional brain connectivity predicts new language learning success in adults

III.1. Preface

The first study established how pre-learning structural connectivity could predict improvement on different aspects of language. Thus, for this second study, we were interested in determining the role of intrinsic functional connectivity biomarkers, i.e., focusing on how brain areas work together, rather than how they are physically connected, to predict L2 learning success. In addition, Study 1 examined connectivity separately within each hemisphere, and revealed effects within the left hemisphere only. Despite this, the right hemisphere is known to play an important role in L2 acquisition and, therefore, for this study we sought to investigate how its interactions with the left hemisphere might relate to individual language learning abilities. This complements Study 1 by demonstrating that pre-existing brain function also plays a role in individual L2 learning ability, as well as showing the importance of communication between the hemispheres. Moreover, the study aims to corroborate the findings from Study 1 that different brain connections, this time functional, may differentiate the ability to learn different language components.

III.2. Main manuscript

Kaija Sander, Xiaoqian Chai, Elise B Barbeau, Shanna Kousaie, Michael Petrides, Shari Baum, Denise Klein, Interhemispheric functional brain connectivity predicts new language learning success in adults, *Cerebral Cortex*, 2022, bhac131. Reproduced with permission from Oxford University Press.

Abstract

Investigating interhemispheric interactions between homologous cortical regions during language processing is of interest. Despite prevalent left hemisphere lateralization of language, the right hemisphere also plays an important role and interhemispheric connectivity is influenced by language experience and is implicated in second language (L2) acquisition. Regions involved in language processing have differential connectivity to other cortical regions and to each other, and play specific roles in language. We examined the interhemispheric interactions of subregions of the inferior frontal gyrus (areas 44 and 45), the adjacent area 9/46v in the middle frontal gyrus, the superior temporal gyrus (STG), and the posterior inferior parietal lobule (pIPL) in relation to distinct and specific aspects of L2 learning success. The results indicated that the connectivity between left and right areas 44 and 9/46v predicted improvement in sentence repetition, connectivity between left and right area 45 and mid-STG predicted improvement in auditory comprehension, and connectivity between left and right pIPL predicted improvement in reading speed. We show interhemispheric interactions in the specific context of facilitating performance in adult L2 acquisition that follow an anterior to posterior gradient in the brain, and are consistent with the respective roles of these regions in language processing.

Introduction

The notion of involvement of bilateral brain networks in language processing is becoming more established in the literature. Although leftward asymmetric lateralization of language in most of the population is well established (Geschwind 1970; Geschwind and Galaburda 1985; Friederici 2011), the extent of participation of each cerebral hemisphere depends on the nature of the task (Chang and Lambon Ralph 2020). An increasing body of research is identifying the role that the right hemisphere (RH) plays in language (Vigneau et al. 2011; Van Ettinger-Veenstra et al. 2012), especially in the context of second language (L2) learning (see Qi and Legault 2020 for review). In particular, it is currently thought that the RH is involved in the early stages of L2 learning (Qi et al. 2015; Xiang et al. 2015; Kepinska et al. 2018), when proficiency is lower (Reiterer et al. 2009; Sebastian et al. 2011). Although much research has been carried out to characterize the contributions of each cerebral hemisphere to language, it is less well understood how the 2 hemispheres communicate with each other to achieve complex cognitive operations. It is, therefore, of interest to understand how the 2 hemispheres communicate and cooperate in the context of language processing and L2 learning (Perrone-Bertolotti et al. 2013a).

Examining how various brain regions function together to enable specific cognitive processing is of importance in developing a comprehensive model of language organization in the brain. The use of functional magnetic resonance imaging (fMRI) allows us to examine functional connectivity (FC) between cortical areas by looking at the temporal correlation between the blood oxygen level-dependent (BOLD) signals of specific voxels in brain regions. It is known that

there is strong FC between homologous regions of the 2 hemispheres (Stark et al. 2008; Roland et al. 2017), which is partly preserved even in individuals in whom there is an absence of the corpus callosum (CC), indicating that homologous regions also communicate via indirect pathways (Tyszka et al. 2011; Siffredi et al. 2021). Thus, interhemispheric connectivity refers to regions between the hemispheres that function together, whether this interaction is mediated by direct anatomical connections or not. There are competing theories regarding whether the interhemispheric interactions are inhibitory (one hemisphere inhibiting the other when performing a task) or excitatory (information being transferred and integrated between the hemispheres to perform certain tasks), with some agreeing that both may be true depending on the processing demands of the task being carried out (see van der Knaap and van der Ham 2011; Kasselimis and Nidos 2015, for review). In terms of functional outcomes of interactions between the hemispheres, it has been established for some time that interhemispheric interaction can facilitate performance, particularly during demanding tasks (Banich 1998; Scalf et al. 2009; Höller-Wallscheid et al. 2017). Indeed, transferring information between the hemispheres, and thus bilateral neural recruitment, may be advantageous to perform complex cognitive tasks (Kasselimis and Nidos 2015). Thus, interhemispheric connectivity, as measured by fMRI, may represent the degree of communication and integration between the hemispheres required for specific functions (Jin et al. 2020). In the context of the language network, evidence shows that interhemispheric interactions occur and are beneficial for language processing. Bilateral activations may represent evidence that information is being integrated between them (van der Knaap and van der Ham 2011; Vigneau et al. 2011).

Functional connectivity at rest (rsFC) is thought to reflect intrinsic properties of brain regions communicating and functioning together (Fox and Raichle 2007). Previous studies have linked rsFC with individual predispositions towards various skills and abilities such as motor learning (Mary et al. 2017), working memory (Fang et al. 2016; Avery et al. 2020), creativity (Cousijn et al. 2014; Bashwiner et al. 2020), learning of certain musical aspects (Hou et al. 2015; Lumaca et al. 2019), different forms of intelligence (Shearer 2020), and language learning (Wang et al. 2012; Ventura-Campos et al. 2013; Chai et al. 2016). In addition, rsFC between homologous regions in each hemisphere is thought to reflect interhemispheric functional integration (Jin et al. 2020), and measuring it could inform us about how interhemispheric functional integration can support cognitive processes, such as learning (Gee et al. 2011; Jin et al. 2020). Thus, examining the relationship between interhemispheric rsFC and L2 learning success could help elucidate whether certain individuals with stronger rsFC have an advantage in acquiring various aspects of a new language. Several studies have examined interhemispheric interaction in the specific context of facilitating performance, including language proficiency. One meta-analysis looking at the link between interhemispheric interaction and language proficiency reported that RH activation during phonological and lexico-semantic processing mainly occurred at the same time as LH activation, indicating some level of interhemispheric interaction (Vigneau et al. 2011). In addition, studies in healthy children have shown that higher interhemispheric FC is related to verbal fluency and vocabulary (Bartha-Doering, Kollndorfer, et al. 2021a) and, furthermore, children with agenesis of the CC exhibit reduced interhemispheric connectivity and lower verbal abilities (Bartha-Doering, Schwartz, et al. 2021b). There is also evidence linking bilingual experience with interhemispheric interaction, in terms of behavior (divided visual field

experiment, Ibrahim 2009), structural connectivity (Coggins III et al. 2004; Felton et al. 2017), and FC (Berken et al. 2016). These studies highlight the link between the strength of interhemispheric interaction and proficiency in a second language. Structural connectivity findings indicate that the anterior mid-section of the CC is larger in bilingual individuals than monolingual individuals (Coggins III et al. 2004; Felton et al. 2017) and rsFC has been found to be stronger between the left and right inferior frontal gyrus (IFG) in bilinguals who acquired their L2 earlier (Berken et al. 2016). Furthermore, a few studies have shown that interhemispheric interactions relate to L2 acquisition ability and influence the acquisition process (Veroude et al. 2010; Schlegel et al. 2012; Xiang et al. 2012; Qi et al. 2019). In terms of structural connectivity, Xiang et al. (2012) report that some aspects of language ability are mediated by interhemispheric connectivity between the left and right IFG, and Schlegel et al. (2012) found that second language learners of Chinese showed increases in fractional anisotropy (FA) in the genu of the CC after language training. In terms of FC, Veroude et al. (2010) reported stronger post-learning increases in FC between the supramarginal gyri in the left and right hemispheres for better learners, whereas Qi et al. (2019) found increases in rsFC between the left and right IFGs post-learning. Although these studies provide evidence of the importance of interhemispheric connectivity in language learning, specific investigations into the role of interhemispheric interactions in various aspects of language are still lacking, and much remains to be understood concerning the role of connectivity between specific regions.

The present study aimed to investigate the facilitative and predictive role of intrinsic interhemispheric interaction in second language learning by examining interhemispheric

connectivity of several perisylvian brain regions in relation to different aspects of language. Although previous studies have reported changes in interhemispheric connectivity as a result of L2 learning (Veroude et al. 2010; Schlegel et al. 2012; Qi et al. 2019), the focus of the present investigation is on predicting L2 learning success based on the connectivity between the hemispheres. Specifically, we were interested in examining the distinct contributions of language-related regions in the inferior frontal lobe, namely area 44 in the pars opercularis and area 45 in the pars triangularis of the IFG, area 9/46v in the middle frontal gyrus (MFG), as well as the superior temporal gyrus (STG) and the posterior inferior parietal lobule (pIPL) that includes the angular gyrus (AG). These regions are of interest because of their established roles in specific aspects of language. We were particularly interested in investigating different parts of the ventrolateral frontal language region separately, as studies often treat this region as a whole (Xiang et al. 2010), despite evidence that it is composed of distinct cytoarchitectonic areas with differential contribution to language. It is known that area 44 is involved in phonological processing (Heim et al. 2009; Church et al. 2011), articulatory aspects of speech production (Heim et al. 2008; Price 2010; Clos et al. 2013), and phonological working memory (Zurowski et al. 2002), and is strongly connected to area 9/46v (see case 6 in Petrides and Pandya 2002). Areas 46 and 9/46 on the MFG are involved in the monitoring of information in working memory (Petrides 2002) and, given the strong connectivity of 9/46v with area 44 and the adjacent ventral premotor cortex, this specific part of the mid-dorsolateral frontal cortex may be involved in monitoring the articulatory aspects of speech in working memory. On the other hand, there is evidence that area 45 is involved in the active controlled retrieval of information from memory (Klein et al. 1995; Petrides et al. 1995; Heim et al. 2009) and certain

aspects of semantic processing (Dapretto and Bookheimer 1999; Gough et al. 2005; Hagoort 2005; Mainy et al. 2007). Area 45 is connected via the extreme capsule fasciculus (ECF) to the middle part of the STG (mSTG; Petrides and Pandya 1988; Petrides 2014) that plays a role in language comprehension (Friederici 2002; Friederici et al. 2003), particularly spoken language given the involvement of the STG in auditory processing. Finally, the role of the AG in the pIPL in reading has been well established (Seghier 2012), including in relation to language comprehension (Price and Mechelli 2005; Graves et al. 2010), semantic processing (Seghier 2012) and learning to read (Carreiras et al. 2009), as well as predicting improvement in reading speed in an L2 (Barbeau et al. 2017).

We selected 3 distinct measures of L2 learning: (i) Repetition of orally presented sentences as reflected in the percent of words correctly repeated in terms of grammar and pronunciation. This measure involves both speech production and monitoring of the articulatory speech output in working memory and is predicted to engage areas 44 and 9/46v. (ii) Listening comprehension, which requires listening to a story and answering comprehension questions, thus involving auditory comprehension and retrieval of information from memory and is predicted to engage area 45 and the mSTG. Finally, (iii) reading speed (Dehaene et al. 2010), reflected in the number of words per minute in a passage read aloud by participants, which requires sufficient understanding of meaning through reading, involving the pIPL. We hypothesized that intrinsic interhemispheric rsFC in each of these regions of interest (ROIs) would facilitate L2 learning and, therefore, would predict behavioral improvement related to these specific areas of language processing.

Methods

Participants

We recruited 18 participants (mean age 20.8 years ±3.9, range 17–32, 12 females) from a French language-learning course. The course was a university-level course for beginners offered by the McGill French Language Centre, consisting of ~80 h of training over 1 or 2 semesters, focusing on grammar, writing, comprehension, and discussion of both audio passages and written documents to provide comprehensive training. The inclusion criteria for the study were right-handedness, normal or corrected-to-normal vision, no reported hearing impairments, no history of traumatic brain injury, neurological disorders, or conditions incompatible with MRI scanning, as well as having no advanced musical training, because of the known link between musical training and language ability (see Milovanov and Tervaniemi 2011 and Jäncke 2012 for review). Advanced musical training was defined as being a professional or expert musician; participants who did have musical training received it in primary or high school, and of those, none still regularly played at the time of testing. At the time of the study, all participants were McGill University students, studying in English, and were beginner French learners. The participants included 2 subgroups whose native (L1) languages were American English (n = 10) or Mandarin (n = 8) with English being the second language (L2). These participants were selected because they were the largest, most homogeneous groups of eligible participants. Proficiency in a language other than English or Mandarin was an exclusion criterion. No group differences were found in working memory and general intelligence, measured by the Digit Span, Letter-Number Sequencing, and Matrix Reasoning subtests of the WAIS-IV (Wechsler

Adult Intelligence Scale; Wechsler 2008), or in behavioral improvement or rsFC (see Table 1) and, therefore, participants were treated as a single group for all analyses. The present study was approved by the Research Ethics Board of the Montreal Neurological Institute (MNI) and the participants gave informed written consent.

Table 1. Scores for the English L1 and Mandarin L1 subgroups in working memory and general intelligence, behavioral improvement in French and interhemispheric rsFC. Significance of the group comparisons is reported as a *t* statistic (*P* value).

	English L1	**Mandarin L1**	**Significance**
Working memory and general intelligence			
Digit Span: Forward (/16)	11.7 ± 1.70	10.25 ± 1.91	1.7 (0.108)
Digit Span: Backward (/16)	8.6 ± 2.01	9.4 ± 2.07	0.83 (0.420)
Digit Span: Sequencing (/16)	8.3 ± 1.06	8.1 ± 2.30	0.25 (0.809)
Letter-Number Sequencing (/30)	20.1 ± 1.3	19.8 ± 1.3	0.49 (0.633)
Matrix Reasoning (/26)	22.5 ± 1.12	22 ± 1.58	0.79 (0.443)
Improvement in French			
Sentence repetition	11.7 ± 8	7.7 ± 6	1.35 (0.196)
Listening comprehension	17 ± 16.5	11 ± 4.9	1.1 (0.297)
Reading speed	20.3 ± 16.8	14 ± 5.4	1.02 (0.325)
Interhemispheric rsFC			
L – R 45	0.51 ± 0.2	0.65 ± 0.18	−1.48 (0.160)
L – R 44	0.56 ± 0.25	0.65 ± 0.16	−0.8 (0.434)
L – R 9/46v	0.56 ± 0.2	0.4 ± 0.12	1.79 (0.090)
L – R mSTG	1.05 ± 0.29	1.02 ± 0.18	0.26 (0.795)
L – R pIPL	0.78 ± 0.34	0.79 ± 0.19	−0.01 (0.992)

Language tasks

Language abilities were assessed at 2 time points, pre- (time 1) and post- (time 2) language training, i.e. prior to and after completion of the French language course, in both English (control language) and French (trained language). The sentence repetition task was the Recalling Sentences subtest of the Clinical Evaluation of Language Fundamentals (4th edition; Semel et al. 2003). The examiner read 24 sentences aloud, one at a time, to the participants, who repeated each one immediately after hearing it. The responses were recorded and then transcribed in order to calculate the percentage of words correctly repeated (i.e. pronounced comprehensibly and in the correct order in the sentence); the average of all 24 sentences was taken as the sentence repetition score. The transcription was scored by a native Quebec French speaker for accuracy of reproduction, and the scoring was then verified by a second native French speaker with overlap in agreement between raters. The listening comprehension task consisted of auditory presentation of a story followed by 17 comprehension questions about the story (Story Learning and Memory test, adapted versions in English and French from tests in use at the MNI, Wechsler 1987). Participants' responses were recorded, and a score was calculated as the percentage of questions answered correctly (content). The reading speed score was the number of words read per minute from another passage also taken from the same Story Learning and Memory test. Each measure was calculated from French and English versions of the tests at time 1 and time 2, and the difference between the 2 time points was used as a measure of improvement for each language.

Imaging

Acquisition

Imaging data were acquired before the start of the French course (time 1) on a Siemens 3 Tesla MAGNETOM Prisma scanner at the McConnell Brain Imaging Centre of the MNI. Resting-state fMRI data were acquired using multi-band echo-planar imaging (EPI; acceleration factor = 6, = time repetition [TR] = 930 ms, time echo [TE] = 30 ms, 72 slices 2 mm thick, and voxel size = 2 mm3) for 10 min while participants focused on a fixation cross on the screen. High-resolution T1-weighted images were obtained using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TR = 2,300 ms; TE = 2.96 ms; flip angle = 9°; 192 slices; and voxel size = 1 mm3).

Analysis

The resting-state fMRI data were preprocessed using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK) using standard preprocessing steps. Images underwent realignment and unwarping, normalizing in MNI space, and smoothing with a 6-mm kernel. Motion outlier images were detected using ART (Artifact Detection Tools) and defined as images that deviated by >3 SDs from the mean image intensity of the session or having composite head movement exceeding 1 mm from the previous image (Whitfield-Gabrieli and Nieto-Castanon 2012; Nieto-Castanon 2020). Denoising of the fMRI time series and FC analysis were performed using the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon 2012). Anatomical CompCor method (aCompCor, Behzadi et al. 2007) was applied to reduce physiological noise in the resting-state

data. Specifically, 5 principal components of the eroded masks of white matter and CSF were included as regressors in the general linear model to achieve optimal noise reduction (Chai et al. 2012). A temporal bandpass filter of 0.008–0.09 Hz was applied to the time series. Regressors for outlier timepoints and head motion parameters were included in the general linear model to account for motion-related artifacts. An ROI-to-ROI FC analysis was carried out to examine specific FC between the regions of interest and their RH homologues, i.e. the temporal correlations between the BOLD signal in a chosen ROI and that in other target ROIs were computed. FC values (Fisher's Z scores of the Pearson's correlation coefficient) between the selected ROIs and their targets were extracted for each participant.

Regions of interest

The ROIs were selected based on a priori knowledge of cytoarchitecture and anatomical connectivity in the ventrolateral frontal cortex (Petrides et al. 2012; Petrides 2014), the STG (Petrides and Pandya 1988, 2009; Petrides 2014), and inferior parietal lobule (Petrides and Pandya 2009; Petrides 2014). We used parcellations of the IFG pars triangularis (area 45) and pars opercularis (area 44) from the Harvard-Oxford atlas that is implemented in the Conn toolbox (Whitfield-Gabrieli and Nieto-Castanon 2012). Given that this atlas has only a parcellation for the whole MFG, and that 9/46v is a specific part of the MFG, we created a smaller ROI in order to look at its FC. This ROI was defined by the inferior frontal sulcus ventrally, the anterior segment of the posterior middle frontal sulcus anteriorly and the intermediate segment of the posterior middle frontal sulcus posteriorly (Petrides 2019). In addition, the Harvard-Oxford atlas only has parcellations for the anterior and posterior STG and

therefore we created one for the middle STG. The middle STG region included the superior temporal sulcus (STS), using Heschl's gyrus as the posterior limit. We also created a specific ROI in the posterior part of the inferior parietal lobule (pIPL), extending from the posterior border of the supramarginal gyrus to the AG as far as the angular sulcus (caudal superior temporal sulcus 2nd ramus, ans/csts2; Petrides 2019), mostly encompassing the AG as well as the most posterior border of the SMG. The area 9/46v, mSTG and AG ROIs were hand-drawn within the previously defined limits using the ROI tool in MRView (Tournier et al. 2019). The ROIs are shown in Fig. 1, and their MNI coordinates (center of gravity) and volumes can be found in Table 2. Since the interhemispheric connectivity of the different regions was compared with behavioral improvement and not directly to each other, the minor differences in volume (which can vary even within an atlas) are not considered to affect the interpretation of the results. Additional ROIs were created as 6-mm spheres for the left (center coordinates: −36 −22 56) and right (center coordinates: 36 −20 58) hand motor regions as nonlanguage ROIs to serve as control areas.

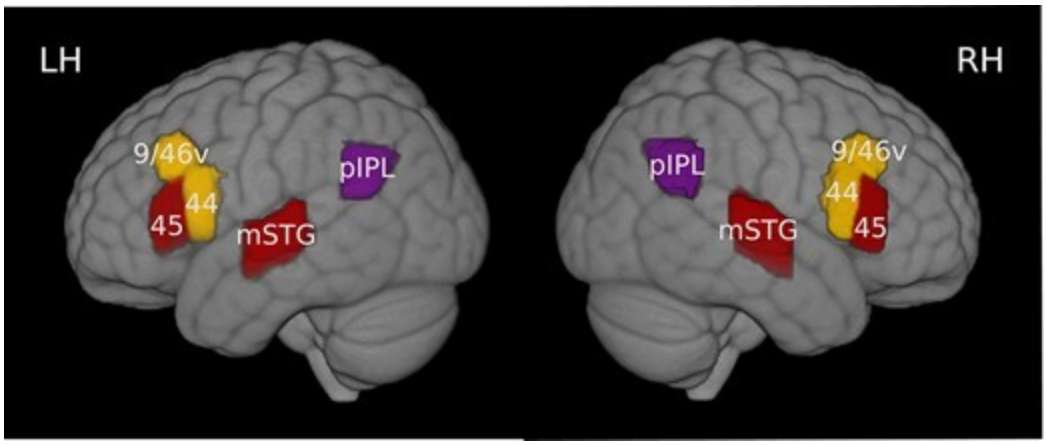

Figure 1. Illustration of the ROIs used to extract interhemispheric rsFC in each hemisphere. Area 9/46v and area 44 are in yellow, areas 45 and the mSTG are in red, and the pIPL is in purple. LH = left hemisphere, RH = right hemisphere, mSTG = middle superior temporal gyrus, pIPL = posterior inferior parietal lobule, 9/46v = area 9/46v, 45 = area 45, 44 = area 44.

Table 2. MNI coordinates (mm) and volumes (mm3) for the ROIs used.

ROI	**Left**				**Right**			
	x	*y*	*z*	Volume	*x*	*y*	*z*	Volume
45	−50	29	19	5,197	52	28	18	4,306
44	−51	16	25	6,170	52	15	26	5,504
9/46v	−45	26	33	5,784	47	24	32	4,456
mSTG	−56	−18	−0.5	16,648	56	−19	2	16,184
pIPL	−56	−54	28	8,208	58	−52	29	7,968

Statistical methods

Paired t-tests were conducted to compare performance from time 1 to time 2 for each behavioral measure. We tested the hypothesized relationships between interhemispheric rsFC at time 1 and behavioral improvement (time 2–time 1) using Pearson correlations based on our specific hypotheses. Specifically, we tested the area 45 and mSTG interhemispheric rsFC values in relation to L2 improvement in listening comprehension, area 44 and 9/46v values in relation to improvement in L2 sentence repetition and pIPL interhemispheric FC in relation to improvement in L2 reading speed. The reported P-values for correlations of the hypothesized rsFC-behavioral improvement relationships of interest are corrected for multiple comparisons (FDR). Assumptions of level of measurement, linearity, normality, and related pairs were met. Nonparametric testing using the bootstrap method (resampling with replacement with 1,000 iterations) was also used to confirm findings, as implemented by the boot function (Davison and Hinkley 1997; Canty and Ripley 2021) in R (R Core Team 2020). Differences in correlation coefficients between male and female participants were tested because of some reports of sex differences in language lateralization (Bitan et al. 2010; Scheuringer et al. 2020), using Fisher r-to-z transformations.

Results

Behavioral results

As expected, there was no improvement in the control language, English, between time 1 and time 2 on any of the behavioral measures (Table 3). However, there was significant

improvement in the language of training, French, after learning, for all 3 measures, as shown in Table 3.

Table 3. Mean ± SD for the behavioral measures: percentage of words correctly repeated for sentence repetition, percentage of questions correctly answered for listening comprehension, and words per minute for reading speed. *T* statistics (*P* values) [Cohen's *d*] are also reported.

	Sentence repetition		**Listening comprehension**		**Reading speed**	
	French	English	French	English	French	English
Time 1	26 ± 7.8	97.3 ± 3	11.7 ± 10	60 ± 26	74 ± 19.8	169 ± 39
Time 2	36 ± 10	96.8 ± 2	26 ± 16.8	64 ± 20	91 ± 16	160 ± 32
Significance	−5.68 (<0.00003) [1.12]	0.69 (0.502) [0.20]	−4.77 (<0.0002) [1.03]	−0.9 (0.375) [0.16]	−5.69 (<0.00003) [0.94]	1.76 (0.09) [0.25]

* It should be noted that, at the individual level, one participant has a negative improvement score for sentence repetition improvement, and another for reading speed. It seems unlikely that the performance of these individuals decreased after language learning, and rather means that their improvement after the course was minimal and their performance on the day of testing happened to be worse. We chose to include all our participants in the analysis as they represent the full range of learning performance.

Pre-learning interhemispheric connectivity predicts language improvement

Areas 44 and 9/46v in relation to sentence repetition

There were positive correlations specifically between the interhemispheric rsFC of area 44 and of area 9/46v with improvement in sentence repetition in French (r = 0.48, P = 0.043 and r = 0.52, P = 0.05, respectively; see Fig. 2). Thus, individuals with higher rsFC between left and right areas 44 and left and right areas 9/46v showed greater improvement in the ability to repeat sentences in French correctly immediately after hearing them. Importantly, these relationships were specific to sentence repetition improvement. Comprehension improvement was not significantly related to interhemispheric connectivity of either area 44 (r = 0.15, P = 0.551) or area 9/46v (r = 0.19, P = 0.447). Likewise, reading speed improvement was not significantly related to interhemispheric connectivity of either area 44 (r = 0.28, P = 0.261) or area 9/46v (r = 0.25, P = 0.313). There were no differences between male and female participants (z = 0.7, P = 0.48, and z = 1.37, P = 0.17, respectively).

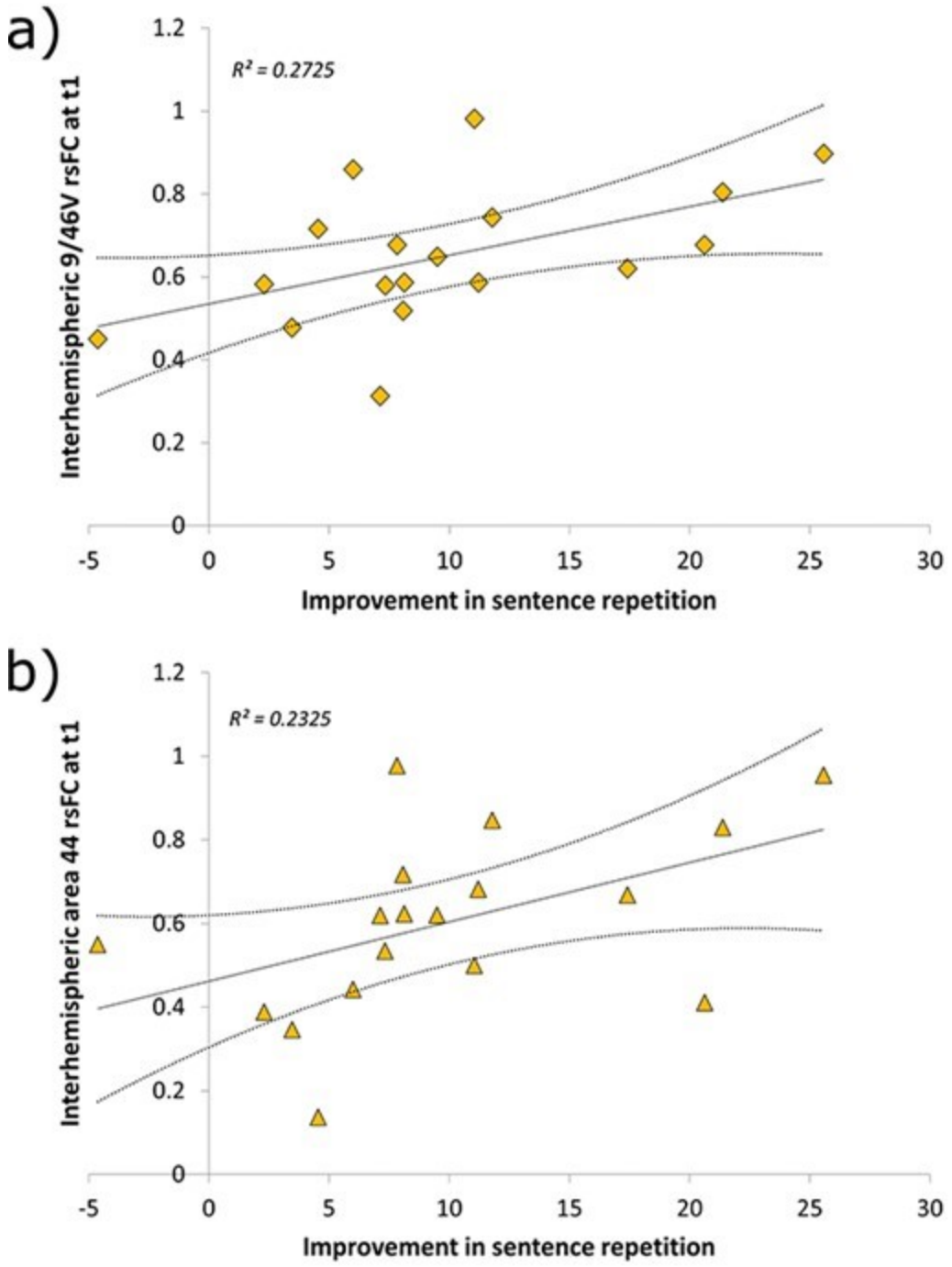

Figure 2. Relationship between pre-learning (*t*1) interhemispheric resting-state connectivity of a) area 9/46v and b) area 44 and improvement in sentence repetition (change in percentage of words correctly repeated) with 95% confidence intervals.

Area 45 and mSTG in relation to listening comprehension

There were specific positive correlations between area 45 and mSTG interhemispheric rsFC and improvement in listening comprehension in French (r = 0.55, P = 0.018 and r = 0.57, P = 0.026, respectively; see Fig. 3). Individuals with higher pre-learning rsFC between the left and right area 45, as well as between the left and right mSTG, demonstrated greater improvement, as indicated by the higher percentage of questions that were correctly answered after listening to a story in French. Critically, these correlations were specific to improvement in listening comprehension. Sentence repetition was not related to interhemispheric connectivity of area 45 (r = 0.33, P = 0.176) or mSTG (r = 0.34, P = 0.172). Nor was reading speed related to interhemispheric connectivity of area 45 (r = 0.39, P = 0.109) or mSTG (r = 0.2, P = 0.433). There were no differences between male and female participants (z = 0.84, P = 0.4 for area 45 and z = −1.2, P = 0.23 for mSTG).

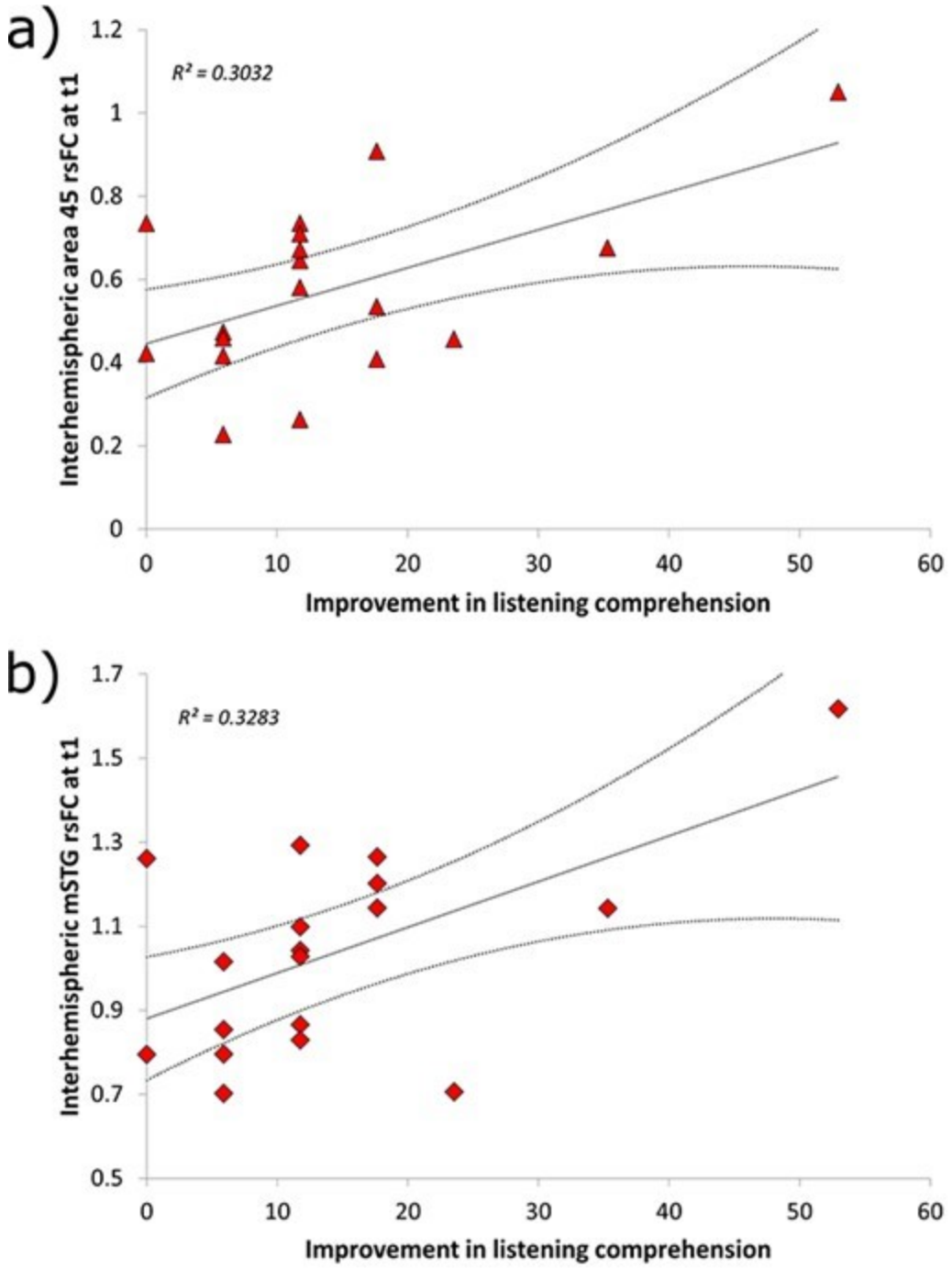

Figure 3. Relationship between pre-learning (*t*1) interhemispheric resting-state connectivity of a) area 45 and b) the mSTG and improvement in listening comprehension (change in percentage of questions correctly answered) with 95% confidence intervals.

pIPL and reading speed

The interhemispheric rsFC of the pIPL pre-learning was significantly and specifically correlated with improvement in reading speed (r = 0.5, P = 0.041; see Fig. 4). Individuals with higher rsFC between the angular gyri of left and right hemispheres improved more in the number of words read per minute while reading a passage aloud. This result was specific to improvement in reading speed (r = 0.37, P = 0.126 for sentence repetition and r = 0.45, P = 0.06 for comprehension). There were no differences between male and female participants (z = 0.67, P = 0.50).

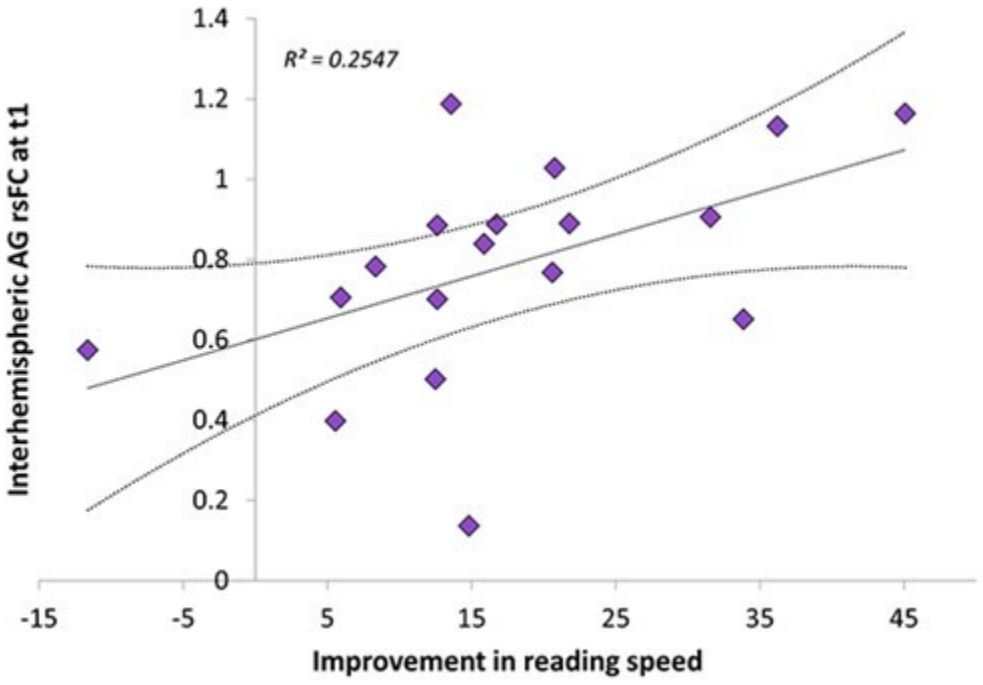

Figure 4. Relationship between pre-learning (t1) interhemispheric resting-state connectivity of the pIPL and improvement in reading speed (change in number of words per minute) with 95% confidence intervals.

Additional results

Nonparametric testing using bootstrapping corroborates the above reported findings. All hypothesized brain connectivity-behavior relationships reported above were significant (Ps < 0.05). The distribution of correlation coefficients from the bootstrap procedure yielded a single peak for all hypothesized connectivity-behavior relationships, which suggests that the correlations do not appear to be driven by outliers (Singh and Xie 2003). Analyses using the interhemispheric rsFC of the control hand motor regions showed no significant correlations with any of the behavioral improvement measures (sentence repetition: $r = 0.08$, listening comprehension: $r = -0.012$, and reading speed: $r = 0.04$). In addition, no significant relationships were found between pre-learning interhemispheric rsFC and pre-learning language abilities (area 44—sentence repetition: $r = -0.27$, area 9/46v—sentence repetition: $r = 0.1$, area 45—listening comprehension: $r = -0.22$, mSTG—listening comprehension: $r = 0.35$ and AG—reading speed: $r = -0.041$).

Discussion

Although functional hemispheric asymmetries have long been demonstrated to be important for different aspects of cognitive processing (Gazzaniga 2000), there is increasing evidence for how the 2 cerebral hemispheres work together. In the context of language processing, few studies have provided direct examinations of the role of interhemispheric communication and connectivity in learning a new language. The results from the present study suggest that greater interhemispheric connectivity pre-learning predicts learning success of a new language in adults

and that this connectivity is predictive of success in specific aspects of language learning. The location in terms of the connectivity between language-related areas follows an anterior to posterior pattern, in line with the predicted functional roles of cortical areas in language. Individuals with higher rsFC between the left and right areas 44 and left and right 9/46v improved more in sentence repetition, those with higher rsFC between left and right areas 45 and left and right mSTG improved more in listening comprehension, and those with higher rsFC between left and right pIPL improved more in reading speed. Importantly, these patterns of correlation were exclusive to these ROIs and the corresponding aspects of language, and behavioral improvement was specific to the trained language, French. In addition, there were no differences between participants whose L1 was English or Mandarin, suggesting that these findings hold true regardless of language background and whether French was a second or third language. These results indicate not only that individual interhemispheric FC overall is an important factor associated with more effective learning of a new language, but that connectivity between distinct language regions in each hemisphere plays a role in promoting learning of specific aspects of the new language.

Sentence repetition has long been used to assess language abilities in various contexts (Klem et al. 2015; Andreou et al. 2021). Since we measured performance as the percent of words correctly repeated, we hypothesized that performance in this task would relate to brain regions involved in articulation, speech production and working memory. Area 44 is known to be involved in various aspects of speech production, such as phonological processing (Heim et al. 2008; Heim et al. 2009; Church et al. 2011; Clos et al. 2013), articulatory planning (Papoutsi et

al. 2009; Price 2010), and other motor aspects of language (Horwitz et al. 2003; Nakajima et al. 2020). Of particular interest was the finding with regard to area 9/46v. The mid-dorsolateral prefrontal cortex (areas 46 and 9/46) is known to play a critical role in the monitoring of information in working memory (Petrides 2000) and, therefore, it was of interest that the ventral part of this region, area 9/46v, which is strongly connected with area 44 and the ventral part of the premotor cortex that controls the orofacial musculature (Petrides 2015), was here shown to be involved in the monitoring of the articulatory aspects of speech in working memory. Thus, better communication between left and right areas 44 and 9/46v could support improvements in working memory and speech production in a new language, which is consistent with the literature and the present findings.

The listening comprehension task required auditory comprehension and retrieval of relevant information. Listening comprehension is known to elicit bilateral activations (Jung-Beeman 2005; Price 2010; Friederici 2011; Vigneau et al. 2011) and to involve the ventral stream of language processing (Hickok and Poeppel 2004; Saur et al. 2008) that is mediated by the temporo-frontal ECF connecting area 45 to the mSTG (Petrides and Pandya 1988; Petrides and Pandya 2009). Area 45 is involved in active controlled retrieval of information from memory (Klein et al. 1995; Petrides et al. 1995; Petrides 2002; Petrides 2006; Heim et al. 2009) and in semantic processing and comprehension (Dapretto and Bookheimer 1999; Gough et al. 2005; Hagoort 2005; Mainy et al. 2007). The STG has a well-established role in auditory processing and comprehension (Friederici et al. 2000; Friederici 2002; Friederici et al. 2003; Gernsbacher and Kaschak 2003). In addition, there is evidence that FC between the left and right pSTG

predicts better receptive language performance in people recovering from brain injury (Dick et al. 2013) and that interhemispheric interactions are important for speech comprehension (Friederici et al. 2007). Thus, stronger interhemispheric rsFC facilitating interactions bilaterally between areas 45 and the mSTG could contribute to improvement in speech comprehension and retrieval from memory.

Finally, the role of the inferior parietal lobule in reading, particularly the AG, is well established (Horwitz et al. 1998; Seghier 2012). Alexia, which affects the ability to read out loud, is commonly associated with lesions of the left AG (Henderson 2014). There is also evidence linking the AG with semantic aspects of reading (Price and Mechelli 2005; Graves et al. 2010), as well as interhemispheric connectivity of the AG with learning to read in late-literate adults (Carreiras et al. 2009). In addition, the posterior part of the SMG, which has some overlap with the angular region of the pIPL, also plays a role in reading (Stoeckel et al. 2009), and activation in the IPL has been found to predict improvement in reading speed after learning French (Barbeau et al. 2017). Thus, stronger interhemispheric pIPL FC may facilitate communication between the pIPLs and thus support improvement in reading abilities in a language that is being learned.

Interhemispheric connectivity and language

The present investigation indicated that the connectivity between each of the above specific cortical regions with their hemispheric homologues in the other hemisphere may play a role in facilitating specific aspects of the learning of a new language. These findings highlight not only

the role of the RH in language learning but also that cooperation between the 2 hemispheres is beneficial. Although there are competing theories regarding the nature of interhemispheric interactions and whether they are inhibitory or excitatory (see, van der Knaap and van der Ham 2011; Kasselimis and Nidos 2015, for reviews), the evidence appears to indicate that cooperation between the hemispheres is advantageous for performance under demanding conditions (Milner 1980; Banich 1998; Scalf et al. 2009; Höller-Wallscheid et al. 2017). Indeed, Milner (1980) reported a marked deficit in the recall of pictures after unilateral temporal lobectomy, suggesting that the successful recall of much of our past experience normally results from the joint participation of the 2 cerebral hemispheres. In addition, data from divided visual field experiments show that interhemispheric interaction increases attentional capacity in visual (Banich 1998) and auditory (Scalf et al. 2009) tasks, whereas fMRI data show that recruitment of homologous regions aids performance in working memory (Höller-Wallscheid et al. 2017). Activation of both hemispheres in various aspects of language processing constitutes evidence that information is being integrated between the 2 hemispheres, at least in this context (van der Knaap and van der Ham 2011). Such findings could mean that individuals with stronger intrinsic interhemispheric rsFC have the best framework to perform well in challenging conditions, which enables them to acquire efficiently various aspects of a new language.

Interhemispheric connectivity has been implicated in several features of general language processing (see Steinmann and Mulert 2012, for review). Several studies show the importance of interhemispheric interaction for speech comprehension (Beeman et al. 2000; Friederici et al. 2007; Sammler et al. 2010), and differences in individual measures of interhemispheric

connectivity have been related to speech perception (Westerhausen et al. 2009). Processing of semantic information compared with perceptual and decision-making information has also been shown to increase interhemispheric cooperation (Perrone-Bertolotti, Lemonnier, and Baciu 2013b). In addition, interhemispheric connectivity relates to verbal fluency (Hines et al. 1992). It is of interest to note that there is a relationship between interhemispheric connectivity and the use of >1 language, i.e. bilingualism. One early study examined the interplay between both hemispheres in bilingual individuals and found that, in the initial stages of L2 learning, the RH plays a more significant role but once the L2 has been mastered, the interaction between the 2 hemispheres is comparable with that in the processing of a native language (L1, Kotik 1983). In terms of structural differences, it has been reported that bilinguals have greater volume in the anterior (Coggins III et al. 2004), mid-anterior and central parts of the CC (Felton et al. 2017), as well as higher FA in the genu, body, and splenium of the CC (Pliatsikas et al. 2015) compared with monolinguals. Other studies have shown that higher FC between the left and right IFG related to earlier age of L2 acquisition in bilinguals (Berken et al. 2016; Gullifer et al. 2018). Taken together, such findings support the proposal that the cognitive demands of managing multiple languages are reflected in how well the hemispheres are able to communicate. Thus, it also seems reasonable that interhemispheric connectivity supports the ability to acquire and manage knowledge of multiple languages. In fact, although our study focused on predicting learning from pre-existing interhemispheric connectivity, several studies have reported changes in interhemispheric connections in relation to L2 learning skills. Specific connectivity between the left and right IFG appears to contribute to some aspects of language learning aptitude (Xiang et al. 2012), as well as learning of a second language (Qi et al. 2019). In

addition, learning of an L2 is associated with higher FA in the genu of the CC (Schlegel et al. 2012) and increases in FC between left and right SMG (Veroude et al. 2010). One study found that faster learners of new phonetic contrasts may have greater interhemispheric connectivity as they tended to have a larger midsagittal area in the middle third of the CC. Furthermore, Antonenko et al. (2012) reported that interhemispheric FC between the inferior frontal gyri was negatively correlated with learning of an artificial grammar, although this study was conducted in older adults who may have somewhat different neural connectivity patterns (Goh 2011), and some evidence shows that bilateral recruitment can actually be beneficial for performance in older adults (Wierenga et al. 2008). Overall, the evidence seems to indicate that learning of a new language is one of the conditions under which cooperation between the hemispheres is beneficial for performance. In a recent review, Qi and Legault (2020) point out that "a dynamic bilateral framework involving neural correlates both within and between the two hemispheres underlies the ultimate success of language learning" (p. 120).

This idea of a bilateral network involved in language is becoming well established and lends further support to the present findings that interhemispheric connectivity can facilitate L2 acquisition. Indeed, the RH has a significant role in language processing and learning, which is important to understand why interhemispheric cooperation matters in the context of L2 learning. The RH is mainly recognized in language for supra-segmental and abstract language processing (Bottini et al. 1994; Beauregard et al. 1997; Buchanan et al. 2000). More recent studies have shown that the RH can be involved in other aspects of language processing, such as sentence and discourse processing (Gernsbacher and Kaschak 2003; Vigneau et al. 2011).

Some have argued that both hemispheres have complementary roles in language processing (Cook 2004). Functional activation in the right frontal and temporal regions has been related to language ability (Van Ettinger-Veenstra et al. 2012). In particular, an early hypothesis explaining the relative role of the hemispheres in the process of L2 acquisition has been that it may mirror that of L1 acquisition in children (Galloway and Krashen 1980; Obler 1981) and that, in the initial stages of learning, there is a shift in laterality from the left to the right hemisphere and a shift back to left hemisphere laterality as proficiency increases. Recent evidence of RH involvement in the early stages of L2 and relationship with L2 proficiency (Reiterer et al. 2009; Qi et al. 2015; Kepinska et al. 2018) appears to support this hypothesis, along with studies that demonstrate aspects of this laterality shift (Hosoda et al. 2013; Xiang et al. 2015; Qi et al. 2019). Thus, the interplay between the hemispheres seems to be a key feature in L2 learning, and it is reasonable that having stronger baseline interhemispheric FC would facilitate this process.

The present study demonstrates that interhemispheric interactions are an important aspect of the L2 learning process and lays the foundation for future investigations into hemispheric dynamics and L2 learning. Future studies using additional measures of language and larger participant samples are necessary to examine further the cooperation of the hemispheres as well as individual patterns of predictors of L2 learning. Moreover, longitudinal studies will be useful to determine whether the relationship between increased interhemispheric FC and L2 improvement persists years after learning and continues to increase with increasing proficiency in the L2 or whether it is a predisposition for better learning abilities that remains stable over time.

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IV. General discussion

The main purpose of this dissertation was to identify structural and functional brain markers that predict specific L2 learning success to help elucidate the neural sources of variability in second language learning outcomes in adulthood. To identify potential biomarkers of L2 learning success, we analysed intrinsic brain connectivity using pre-learning brain scans, with the first study focusing on structural, intra-hemispheric connectivity and the second study focusing on functional, inter-hemispheric connectivity; in both cases, we correlated these measures with improvement in specific aspects of L2 learning. A secondary aim of this dissertation was to address some of the issues in the field of study of L2 learning, as identified in section I.4.1 of the introduction, such as lack of anatomical specificity, the focus on only one aspect of language, and the need for targeted, hypothesis-driven investigations. To do so, we employed a comprehensive approach using anatomically rigorous and refined measures of connectivity bilaterally, as well as fine-grained measures of distinct and varied aspects of language. Both studies presented in this dissertation rely on the same longitudinal paradigm, testing participants taking part in a French learning course. The first study demonstrated a dissociable pattern of structural predictors within specific frontal and parietal regions relating to L2 learning improvement. Specifically, the focus was on connectivity between area 45 and the angular gyrus mediated by the second branch of the superior longitudinal fasciculus (SLF II), which predicted improvement in lexical retrieval, and on connectivity between area 44 and the supramarginal gyrus mediated by SLF III, which predicted improvement in articulation rate. The second study also demonstrated dissociable patterns of L2 learning predictors, this time based

on specific interhemispheric functional connectivity of selected anterior to posterior brain regions relating to the corresponding language aspects hypothesised to improve. That is, interhemispheric connectivity of areas 44 and 9/46v predicted improvement in sentence repetition while that of area 45 and mid-STG predicted improvement in auditory comprehension; finally, interhemispheric functional connectivity of the AG predicted improvement in reading speed. Taken together, these results help further elucidate the neural basis for individual variability in L2 learning. Indeed, variability in L2 learning seems to be linked to individual brain structure and function, as we found different connectivity patterns that can predict specific L2 learning outcomes. The section that follows discusses the specificity of the relationships between brain and behaviour and the importance of detailed yet comprehensive explorations into biomarkers of L2 learning, as well as the broad patterns of inter- and intrahemispheric connectivity related to language learning revealed by the findings, and finally, the remaining questions to be answered by future studies.

IV.1. Specificity

As stated by Feng et al. (2021): “Learning different components of language is associated with partially shared and distinct cognitive and neural processes” (p.7373). This means that elucidating the specific relationships between precise anatomical regions and given language components is crucial. In the present dissertation, anatomical precision is presented as a key aspect of studying language learning, given that regions with different cytoarchitectural and connectivity profiles will likely play different roles in language processing. In addition, we did not restrict our investigation to the classical language regions of the left hemisphere, given the

large emerging literature related to the importance of focusing on networks (Sporns 2011; Eickhoff and Müller 2015; Li and Grant 2016) in both hemispheres (Vigneau et al. 2011). Moreover, obtaining refined yet comprehensive measures of L2 attainment, i.e., measuring specific and diverse components of language, is also crucial when aiming to capture the full range of behavioural functions related to precisely delineated anatomical regions. Based on this, for the purposes of this dissertation, we implemented a method for aligning specific measures of language improvement to anatomical knowledge rooted on cytoarchitectural and macaque tracer studies (Petrides and Pandya 1984; Petrides and Pandya 2002; Petrides 2014a). This enabled us to establish separable patterns of correlations between brain connectivity and learning outcomes, thus allowing us to draw conclusions about the distinct connections that contribute to supporting L2 learning in adulthood.

Examining the connectivity of larger regions that are often studied as a whole, despite known sub-regional cytoarchitectural and connectivity differences helps reveal crucial additional information. For example, in Study 1, the connectivity patterns of the SMG and the AG in the IPL to frontal regions were differentiated and we were thus able to detect differences related to functional language outcomes. This study further elucidated the roles in language of two different elements of the dorsal language stream, with SLF II relating more to lexical aspects of language and SLF III relating more to motor aspects of language (Nakajima et al. 2020; Sander et al. 2021). This is in contrast with much of the literature, where the SLF is merged with the arcuate fasciculus and considered as the AF/SLF dorsal system (see Dick and Tremblay 2012 for discussion), which means that much detail about the functions of these regions and pathways is

missed. Indeed, the AF/SLF system is most often only investigated in relation to conduction aphasia and repetition deficits (Wernicke 1874; Axer et al. 2001; Ardila 2010). Furthermore, this issue of AF/SLF amalgamation is compounded by the fact that one of the predominant models of dorsal white matter connections (Catani et al. 2005) identifies three segments of the AF: a long segment corresponding to the classical AF connecting frontal and temporal regions, a posterior segment connecting temporal and parietal regions, and an anterior segment connecting frontal and parietal regions, which, in fact, corresponds to the SLF. In addition, the dissection protocol for these different segments only requires placing "through" ROIs (i.e., ROIs that capture all the streamlines passing through them) rather than "endpoint" ROIs (i.e., ROIs that capture streamlines terminating within them). This means that the precise termination points of the WM tracts are not determined and thus, no distinctions are made between tracts terminating within subregions of the IFG or the IPL. This model and approach illustrate the AF/SLF amalgamation issue, as well as the lack of specificity between distinct cytoarchitectonic regions that have different connectivity profiles that would allow the branches of the SLF to be reconstructed (Catani et al. 2005). Reconstructing the AF/SLF system as one may also lead to issues with interpretation when studies report findings regarding the AF, which in fact pertain to fronto-parietal connections and thus instead reflect properties of the SLF (Kepinska et al. 2017; Assaneo et al. 2019). In addition, as previously addressed, even studies that do specifically investigate the SLF do not normally separate SLF II and SLF III (Luk et al. 2011; Pliatsikas et al. 2015; Qi et al. 2015; Mamiya et al. 2016). This lack of distinction between the branches of the SLF is also problematic and leads to further issues with interpretation because, as demonstrated in Study 1, the SLF II and III appear to play different roles in language due to

the different regions they connect. These findings emphasise the need to consider cytoarchitectural and connectivity differences in studies linking neuroanatomy to particular behavioural outcomes.

In terms of functional connectivity, Study 2 differentiated areas 44 and 45 of the so-called Broca's area in the IFG and focused on other precisely anatomically-defined regions (area 9/46v, the mSTG and the AG), which also proved to be valuable, as it revealed different roles associated with the interhemispheric connectivity patterns of each region. Indeed, many investigations linking interhemispheric interactions with language experience and abilities focus on broad sub-regions of the CC itself, which does not take into account which cortical regions are connected, rather than on connectivity between specific areas via the CC (Coggins III et al. 2004; Pliatsikas et al. 2015; Felton et al. 2017). While this still provides crucial information about interhemispheric interactions, without knowing precisely which brain areas are interacting, linking these interactions to precise functional outcomes is difficult. In addition, Study 2 highlights the importance of comprehensive investigations of the language network, which include the right hemisphere. The idea of a bilateral network involved in language is well established (Vigneau et al. 2011), and thus understanding how the RH hemisphere interacts with the language dominant LH to support language functions and learning is critical. Long-standing evidence of the role of the RH in language seems to implicate the right hemisphere mainly in supra-segmental and abstract word processing (Bottini et al. 1994; Beauregard et al. 1997; Buchanan et al. 2000). However, more recent studies show the RH is involved in other aspects of language processing, such as sentence and discourse processing (Gernsbacher and

Kaschak 2003; Vigneau et al. 2011); in addition, growing evidence indicates that the RH may work by cooperating with the LH (Vigneau et al. 2011; Qi and Legault 2020), as reflected by bilateral patterns of activation. These hemispheric dynamics are also apparent during L2 learning. Indeed, a systematic review by Qi and Legault (2020) lends support to the finding that learning certain aspects of language is predicted by bilateral brain characteristics and connectivity, as illustrated in Figure IV.1. Thus, more anatomically thorough and informed investigations will ensure these dynamics are taken into consideration, leading to more accurate examinations of L2 acquisition.

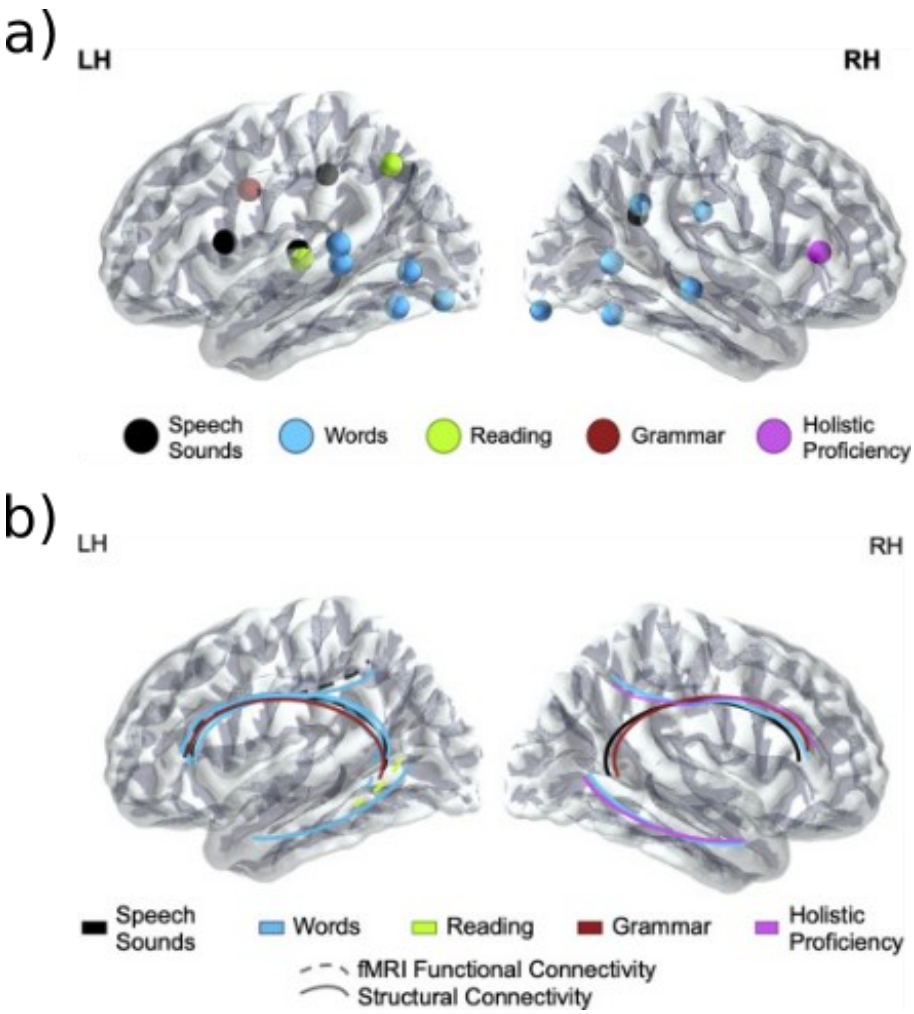

Figure IV.1. a) Bilateral regions predictive of various aspects of language learning. b) Connectivity in each hemisphere predictive of various aspects of language learning. Adapted from: Qi Z, Legault J. 2020. Psychology of Learning and Motivation. Vol. 72. Academic Press. p. 119–163. Copyright © 2020 Elsevier Inc. Adapted with permission.

Going hand in hand with the need for greater anatomical accuracy is the need to have equally refined behavioural measures of distinguishable components of language in order to capture functional differences between closely-related brain regions. However, a large number of studies that have used MRI to find predictors of L2 learning focus only on a single aspect of language learning, with many studies examining learning of pitch patterns (Wong et al. 2007; Wong et al. 2008; Wong et al. 2011; Sheppard et al. 2012), as well as novel phonemes (Golestani et al. 2002; Ventura-Campos et al. 2013), new vocabulary (Veroude et al. 2010; López-Barroso et al. 2013), or more holistic measures, such as grades from language courses (Qi et al. 2015; Mamiya et al. 2016; Qi et al. 2019). This is not to say that such approaches are not valuable to establish relationships between brain regions and the functional processes they support, but specificity of the relationship cannot easily be determined in this way, given variability across individuals and measures. It should also be noted that holistic language measures, i.e., measures evaluating language as a whole, such as course grades, may be useful to establish overall neural patterns relating to global L2 learning success, but have a more limited use in trying to elucidate different aspects of L2 learning or details of the L2 learning process. While no brain-function relationship is exclusive, since no single brain region will support only one function and no function relies on only one brain region, steps may be taken to strengthen conclusions about them. For instance, control measures may be used to infer more conclusively specificity, such as including non-language measures of a control condition (non-language learning), language measures of a non-trained language (the L1) or other measures in the language being trained with minimal overlap (comprehension vs production, for instance) to show the relationship between a brain region and learning of a specific aspect

of the language being trained. In the present studies, this was achieved by examining several brain regions alongside multiple learning aspects hypothesised to be related in both a trained language (French) and a control language not being trained (English). Thus, we were able to demonstrate correlations that were specific to the trained language and between certain regions and the predicted behavioural outcome, which did not relate to results for English language processing or other behavioural measures. Therefore, as well as having a control condition, the different correlations may be considered as controls for each other. Few studies in the literature employ this form of control, with most of the previously-cited studies focusing only on measures of the language being trained (Veroude et al. 2010; Wong et al. 2011; López-Barroso et al. 2013; Qi et al. 2015). As was demonstrated with our findings, even examining multiple measures of the L2 in combination with distinct brain regions can help elucidate whether individual learning abilities are dissociable. To date, few other studies have attempted to investigate multiple biomarkers by dissociating the pre-learning connectivity of distinct language regions as related to improvement in specific, predicted aspects of L2 learning. An example of a study that does establish dissociable relationships between types of L2 learning and neural event-related potential (ERP) patterns is that by Qi et al. (2017), which linked novel vocabulary learning abilities to the N400 effect, while morphosyntactic learning was predicted by the P600 effect. Importantly, the P600 predicted morphosyntactic learning, but not vocabulary learning, while the N400 better predicted vocabulary learning. Some other studies did investigate the learning of more than one sub-skill of language in relation to different neural patterns but did not specifically investigate whether these relationships were dissociable (Chai

et al. 2016). The results presented in this dissertation indicate that biomarkers for language learning seem to depend on the specific type of learning being measured.

Taken together, the findings from both studies presented in this dissertation build on the literature investigating connectivity biomarkers of L2 learning by improving knowledge relating to specific structure-function relations across less explored regions of the language network. Indeed, increased specificity in these investigations not only enabled us to establish novel, highly specific biomarkers but also to demonstrate novel, distinct roles of connectivity via SLF II and SLF III and for specific interhemispheric connectivity in L2 learning. This was possible because using multiple brain regions and a range of language measures allowed us to demonstrate dissociations between the different brain-behaviour relationships.

IV.1.1. Implications

Beyond simply achieving higher accuracy and building more complete models of brain regions supporting various aspects of L2 learning, identifying specific biomarkers of language learning has wider implications. Firstly, identification of biomarkers contributes to addressing the main question posed in this dissertation regarding the neural factors that contribute to individual L2 learning variability. This is particularly important in relation to brain connectivity, as summarised by Sporns (2011): “if patterns of brain connectivity are associated with cognition, then individual variations in brain networks should also be associated with variable cognitive performance” (p.199). Indeed, individual differences in pre-learning brain connectivity appear to constitute predisposing factors for language learning abilities (Zatorre 2013).

Secondly, the ability to predict a wide range of L2 learning outcomes allows for applications tailored on an individual level. Indeed, in recent years, there has been a growing interest in more individualised approaches in a variety of domains and applications, such as personalised medicine (Vogenberg et al. 2010), and, more pertinently, personalised learning (Li and Wong 2021). In the context of new language learning, personalised learning (Wong et al. 2017) has been defined as "a program of research where genetic, neural, and behavioral (e.g., perceptual/cognitive) predictors can be used to customize learning paradigms at the individual level" (Vuong and Wong 2019, p.331). Thus, the goal of determining L2 learning biomarkers goes beyond simply identifying markers of L2 learning attainment, but rather identifying individual characteristics of learning, such as what aspect of language is best or most quickly learned, and how it may be best taught. The personalised learning framework requires three steps that must be carried out so it can be successfully implemented: identifying individual differences in learning, determining factors that can predict these individual differences in learning and, finally, using these predictors to tailor learning programs to individual learners' needs (Wong et al. 2017; Vuong and Wong 2019). Individual differences in language learning attainment have been established for some time (see Birdsong 2004 and Birdsong 2018 for review). Previously described research (see section I.3.2. of the general introduction for more detail) contributes to determining neural predictors of L2 learning, including both structural biomarkers, such as WM properties of the AF predicting word learning (López-Barroso et al. 2013) and of the SLF predicting better grades in a language course (Qi et al. 2015; Mamiya et al. 2016), as well as functional biomarkers such as rsFC between the left anterior insula/frontal

operculum and the left posterior STG predicting vocabulary learning (Chai et al. 2016) and rsFC between the left insula/frontal operculum and the left SPL predicting foreign sound discrimination (Ventura-Campos et al. 2013). Some work has even begun to develop the concept of biomarkers further by establishing "learning profiles", i.e., individual attainment patterns across different language components based on patterns of neural predictors (Feng et al. 2021). For example, Feng and colleagues (2021) investigated four brain networks in relation to the learning of multiple aspects of an artificial language (vocabulary, morphology, and phrase and sentence structures) and found that the dynamics of the networks varied during learning and contributed to predicting individual profiles of learning outcomes (which comprised the learning outcomes across the language components studied). The studies carried out for this dissertation contribute to the idea of learning profiles by attempting to establish multiple dissociable and precise individual markers of L2 learning. Given that we found this regardless of the L1 of the learners, we believe this approach is relevant to all languages. Predictors can also be used to optimise learning, for example, by examining whether individuals with different learning profiles learn better from specific types of instruction. Studies have also begun investigating this issue, comparing the efficacy of different training paradigms on learning of pitch perception and finding that different types of training selectively improve learning in individuals presenting certain pre-learning abilities (Perrachione et al. 2011; Ingvalson et al. 2013). In summary, identifying highly specific and wide-ranging biomarkers of types of L2 learning will help lay the foundation for identifying profiles of language learners in order to implement more individually-suited and effective training approaches.

Finally, research that informs us about brain networks and pathways that facilitate L2 learning can have applications beyond personalised learning, for example, going as far as influencing language teaching policies. Other applications could include clinical applications such as determining factors predicting success in children with learning problems, or in the context of rehabilitation of adults who have suffered a stroke and are left with language impairments. Overall, identifying and predicting individual abilities is useful to improve quality of life and better support people on an individual level, and we can remain hopeful that establishing predictors of successful L2 learning may one day contribute meaningfully to improving people's lives.

IV.2. Hemispheric patterns of biomarkers

The present findings also reveal other interesting information about global patterns of neural connectivity associated with each type of biomarker investigated: intrahemispheric effects for structural connectivity and interhemispheric effects for functional connectivity. While discussing the results of interhemispheric structural connectivity and intrahemispheric rsFC investigations in relation to L2 learning in this participant sample is beyond the scope of this dissertation, it should be noted that those questions were examined but did not yield any significant findings. It therefore seems that thus far, structural connectivity within the left hemisphere and functional connectivity across the hemispheres best predict l2 learning. As previously discussed (see section I.2.1. of the general introduction), the right hemisphere is known to play an important role in language processing and learning. Accordingly, the investigations of the roles of SLF II and III in L2 learning in Study 1 were conducted bilaterally,

though no effects were found within the RH. This prompted further investigation into the possibility that one key way the RH plays a role in L2 acquisition is through its functional interactions with the LH. Thus, in Study 2, interhemispheric connectivity was examined in relation to L2 learning. The following sections consider potential reasons why these different patterns of hemispheric connectivity were detected using different approaches to the study of neural connectivity.

IV.2.1. Methodological considerations

This section aims to outline potential methodological reasons for the different hemispheric patterns between structural and functional biomarkers. The fact that structural investigations using dMRI tractography revealed that intrahemispheric connectivity is a predictor of L2 learning, while functional investigations using rsFC revealed that interhemispheric connectivity predicts language learning may be due to the nature of the methods used. Indeed, these different patterns may not necessarily reflect hemispheric dissociations between structural and functional biomarkers, but rather may reflect the fact that each method is best suited to detect specific effects. As discussed in the general introduction, while presumably brain function is dependent on brain structure, current imaging methods do not seem to fully capture this relationship. This could be due to functional connectivity being mediated by indirect anatomical connections that are not adequately captured using tractography or being affected by cognitive states unrelated to anatomical connections (Skudlarski et al. 2008). In the context of this dissertation, we could, for instance, surmise that interhemispheric rsFC is not directly mediated by the CC (i.e., indirect pathways through other cortical regions or subcortical structures) or

that interhemispheric connectivity between specific regions is more difficult to capture with tractography dissections of the CC. Indeed, many language studies investigating the role of the CC in language learning either focus on the whole CC (Elmer et al. 2011; Pliatsikas et al. 2015), or sub-sections (Coggins III et al. 2004; Felton et al. 2017), but not specific terminations at the border with the grey matter within each hemisphere. Alternatively, it could be that in the case of functional intrahemispheric connectivity, though communication between key language regions within a hemisphere may still be relevant to the L2 acquisition process, the rsFC between them happens not to be the best predictor of successful attainment, or that the rsFC relates to other linguistic factors not investigated here.

In addition, observed differences between structural and functional predictors may be due to imaging indices themselves, and the biological mechanisms they may reflect. The issues linked to interpreting brain imaging measures are discussed in sections I.1.2 and I.1.3 of the general introduction. In brief, diffusion MRI relies on the diffusion rate of water in various tissues and how constrained the movement of water may be by anatomical structures within the tissue (Soares et al. 2013), while resting-state fMRI is dependent on the coupling between neuronal activity and the corresponding flow of oxygenated blood, i.e. the BOLD signal (Soares et al. 2016). Thus, it is evident that both methods measure different processes with different interpretations that are not necessarily directly related. Commonly-used measures derived from dMRI, such as FA, cannot directly be related to a single specific microstructural anatomical feature, and likely reflect a combination of features such as membrane integrity, myelin thickness, and axon diameter and density (Beaulieu 2014). On the other hand, rsFC measures the temporal correlation of the BOLD signal between two given regions, and therefore is

thought to reflect neuronal metabolism (Eickhoff and Müller 2015). Thus, it is not necessarily surprising that the relationship between brain structure and function is not adequately captured by comparing indices of axonal microstructure to the ratio of oxy-/deoxy-haemoglobin in the blood.

IV.2.2. Neurobiological considerations

Beyond the way different indices of brain connectivity are measured, there could also be some neurobiological reasons for which differential hemispheric patterns of structural and functional predictors were found. Indeed, the way structure and function develop within the brain could explain why the two types of biomarkers present differently. Brain structure, including white matter pathways, are already established at birth (Gilmore et al. 2018). Functional connectivity on the other hand, seems to be more plastic throughout development, with higher-order networks emerging in the first two years of life (Gilmore et al. 2018) and continuing to change throughout the lifespan (Edde et al. 2021). Thus, it could be said that brain structure tends to be genetically determined (Thompson et al. 2001), although structural plasticity does occur, with genetic factors having been shown to account for 75-90% of the variance in FA, and could influence the link between FA and cognitive factors (Chiang et al. 2009; Johansen-Berg 2010), while brain function develops and changes with experience (Edde et al. 2021).

Consistency with global patterns of neural changes with L2 learning

As discussed in section 1.3.1 of the introduction, changes occur with L2 learning in and between specific brain regions, and, taken together, can help elucidate global patterns of change

throughout the brain. One such global pattern is the shift in laterality as L2 proficiency increases, from the left to the right hemisphere in the early stages of L2 learning (Reiterer et al. 2009; Qi et al. 2015; Kepinska et al. 2018), followed by a shift back to left hemisphere laterality (Hosoda et al. 2013; Xiang et al. 2015; Qi et al. 2019). This pattern illustrates that the interplay in connectivity within and between the hemispheres seems to be a meaningful feature in L2 learning. This evidence of a laterality shift combined with information about how brain structure and function develop is consistent with our findings that L2 learning is best predicted by left intrahemispheric structural connectivity and interhemispheric functional connectivity. Indeed, structural connectivity of the language regions would be optimised from birth for LH specialisation and thus be the best predictor of L2 learning. In contrast, functional connectivity is more adaptable and thus may better reflect recruitment of the RH as it becomes increasingly relevant with L2 learning. Therefore, having stronger pre-learning connectivity between the hemispheres would be advantageous to promote the role of the RH in early stages of L2 acquisition and thus support more successful learning.

IV.3. Future directions: remaining questions

The studies presented in this dissertation aimed to further our understanding of individual neural factors that contribute to variability in L2 learning outcomes. Whereas the resulting findings do contribute to this goal when considering existing limitations in the current literature, more in-depth questions have yet to be answered. The following section discusses some of the questions about successful L2 learning that remain unanswered.

IV.3.1. Universality of findings

The participants taking part in these studies were all beginner learners of French but were also part of different subgroups based on their language background: 10 participants had English as their L1 while 8 participants had Mandarin as their L1 and English as their L2. This provided the opportunity to examine the effects of being bilingual on learning a third language and to make cross-language comparisons between learners with different language backgrounds. Indeed, evidence does indicate that in late learners, L2 learning occurs around and must adapt to an established L1 and thus is more dependent on the specific L1 (Alonso 2016; Hernandez 2016). However, from the (admittedly limited) present findings, we can conclude that neural connectivity predictive of L2 learning seems to be independent of language background, as results did not differ between the English and Mandarin L1 groups. Thus, there appears to be some universality to these learning biomarkers, at least for the early stages of L2 learning.

However, the sample size is relatively small, implying that each L1 subgroup is quite constrained. Low sample sizes have long been identified as an issue in neuroimaging studies (Szucs and Ioannidis 2020), leading to low replicability of findings (Button et al. 2013; Turner et al. 2018). An obvious solution to increase replicability of findings is to reproduce this study design with more participants in the whole group and balanced between L1 backgrounds. Since obtaining larger sample sizes can be costly and may not be feasible, alternative solutions to increasing statistical power for detecting brain-behaviour relationships have been proposed, such as using reliable behavioural and neural measures, and behaviourally screening participants prior to brain scanning in order to select groups containing more extreme values

(de Haas 2018). Thus, future studies will have to consider incorporating larger sample sizes and carefully selecting behavioural and neural measures as well as participants in order to strengthen conclusions about the universality of these findings and further probe the influence of language background on neural predictors of learning.

IV.3.2. Other sources of variability in L2 learning

Although the present findings do help to identify the contributions of intrinsic neural connectivity to individual L2 learning abilities, there are undoubtedly many other factors that contribute to L2 learning success. As previously mentioned, native language background likely plays a role in the new language acquisition process. In addition, neurogenetic factors that may predispose individuals to better learning may play a role. Some studies have already begun to untangle how specific genes may have an effect on L2 learning achievement through their potential influences on brain structure and function (Wong et al. 2012; Mamiya et al. 2016). Other cognitive factors are also known to predict L2 learning abilities, such as working memory (Linck and Weiss 2011) and cognitive control (Luque and Morgan-Short 2021). Given the many potential brain-related sources of L2 learning abilities and the many ways in which those factors may interact, a considerable amount of work is still needed to establish with confidence the relationships between those factors, and thus eventually establish more detailed and comprehensive biomarkers of successful L2 learning. In addition, precisely what biomarkers of L2 learning are predicting needs to be clarified: do they merely predict final attainment or speed of learning (Zatorre 2013)? This is an important element to consider, as this could in turn

have an impact on the potential applications and interventions implemented based on such predictors.

IV.3.3. Plasticity

Finally, a natural question to ask when collecting longitudinal learning data is: what brain changes may occur as a result of learning? While it has been established behaviourally that participants did indeed improve in the tested aspects of the trained language, investigating the neural connectivity changes that occur as a result of this learning was beyond the scope of this dissertation. However, knowing what plastic changes take place and how brain plasticity relates to variability in language learning represents valuable information. Specifically, examining whether changes in the brain relate to specific behavioural improvements could be informative for elucidating the specific functional roles of language-related brain areas in the L2 learning process. One study has reported changes to language WM tracts as a result of overall L2 learning (Schlegel et al. 2012), while functional studies have reported changes in rsFC related to phoneme learning (Ventura-Campos et al. 2013) and vocabulary learning (Veroude et al. 2010). These findings illustrate that much work remains to be done regarding what anatomical and functional neural pathways change with L2 learning, and how they relate to specific behavioural outcomes. Data from our study were also obtained at time 2 of learning for both behavioural and imaging measures and will be of importance for future examination of plasticity of learning in adulthood.

General conclusion

The aim of this dissertation was to further our understanding of individual neural pathway characteristics that contribute to variable second language learning abilities by establishing fine-grained predictors of L2 learning outcomes. Dissociable patterns of structural and functional connectivity biomarkers were demonstrated for distinct aspects of language, both within and across hemispheres. These findings highlight the importance of specific and hypothesis-driven investigations relating neuroanatomy to a range of language components, as well as considering bilateral interactions within the language network, beyond classical left-lateralized language regions. In a wider sense, the role of biomarkers is to predict outcomes based on underlying factors, thus providing the ability to intervene in advance of the outcome and improve people's lives. Neural biomarkers have been shown often to be better predictors of outcomes than more traditional measures (Gabrieli et al. 2015), and have even been described as "a humanitarian and pragmatic contribution of human cognitive neuroscience to society" (Gabrieli et al. 2015, p.11), thus highlighting the importance of this line of work.

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