Neural and behavioral signatures of language control in highly proficient bilinguals: Evidence from healthy individuals and brain tumor patients

Polina Timofeeva

eman ta zabal zazu

Universidad del País Vasco
Euskal Herriko Unibertsitatea

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Neural and behavioral signatures of language control in highly proficient bilinguals: Evidence from healthy individuals and brain tumor patients

Doctoral dissertation by:

Polina Timofeeva

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Supervised by:

Lucia Amoruso

and

Manuel Carreiras

eman ta zabal zazu

Universidad del País Vasco Euskal Herriko Unibertsitatea

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To my family

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RESUMEN EN CASTELLANO

La experiencia bilingüe - el contacto sostenido con una primera (L1) y segunda lengua (L2) - se ha convertido en una habilidad clave en nuestro mundo globalizado, ya que permite a los individuos comunicarse eficazmente en varios idiomas y contextos lingüísticos (Paradis 2000). No obstante, las personas bilingües enfrentan un desafio cognitivo: ser capaces de controlar qué idioma utilizar en una situación determinada, evitando la interferencia del idioma no deseado (Abutalebi and Green 2007, 2008; Green 1998; Kroll and Bialystok 2013). Comúnmente conocido como control del lenguaje, este mecanismo permite a los bilingües alternar adecuadamente entre su L1 y L2 según las necesidades del contexto. A pesar de la amplia investigación sobre el tema, todavía queda mucho por entender acerca de la dinámica neural que subyace a este mecanismo (Gray and Kiran 2016), así como su posible reorganización en presencia de daño cerebral (S Moritz-Gasser and Duffau 2009).

La presente tesis doctoral aborda dos preguntas principales: 1) ¿Cuáles son los correlatos espectro-temporales y espaciales que subyacen al control del lenguaje en la población bilingüe sana? 2) ¿Qué sucede cuando el cerebro bilingüe debe negociar el control del lenguaje en presencia de un tumor? Para responder a estas preguntas, se realizaron cuatro experimentos. En dichos experimentos, se utilizó la misma tarea de cambio de idiomas (language switching), en donde los participantes debían nombrar a viva voz una serie de estímulos (imágenes de objetos) en uno u otro idioma dependiendo de una clave contextual (color). De este modo, en ciertos ensayos los participantes debían nombrar en el mismo idioma utilizado en el ensayo previo (ensayos de no cambio) y, en otros, en un idioma diferente (ensayos de cambio o switch). La diferencia de latencia entre ambos tipos de ensayo se conoce como “coste de cambio” (switch cost) y ha sido ampliamente utilizada como indicador de los procesos de control del lenguaje (Meuter and Allport 1999).

En el Experimento I, la tarea se pilotó de manera conductual, y en el Experimento II, se combinó con el registro simultáneo de señales magnetoencefalográficas (MEG). En ambos casos, se evaluaron grupos independientes de bilingües sanos (hablantes de castellano y euskera), altamente competentes en ambos idiomas. En el Experimento III, se utilizó el mismo paradigma que en el II, pero en este caso se evaluó a un grupo de pacientes bilingües con tumores cerebrales (gliomas de bajo grado) que afectaban áreas críticas para el procesamiento del lenguaje en el hemisferio

izquierdo. Finalmente, en el Experimento IV, se utilizó dicha tarea en un grupo de bilingües altamente competentes hablantes de italiano y friulano. Adicionalmente, se incorporó en este último caso una tarea de control en donde los participantes debían alternar entre nombrar el objeto o una acción asociada al mismo en cada idioma por separado. De este modo, en ciertos bloques los participantes alternaban entre idiomas, mientras que en otros alternaban entre categorías semánticas. Ambas tareas se realizaron en combinación con un enfoque de "lesión virtual" mediante estimulación magnética transcraneal (TMS, según sus siglas en inglés). Este tipo de protocolos permite alterar de manera momentánea la actividad de una región cerebral específica y medir cambios en la conducta asociada a la tarea, lo cual posibilita establecer relaciones causales entre ambas (Bergmann and Hartwigsen 2021). Nos centramos en el giro angular (AG) y el giro temporal medio posterior (pMTG), ya que ambas regiones se han visto involucradas en procesos de control del lenguaje en bilingües (Abutalebi and Green 2016; Hernandez 2013).

En el Experimento I observamos que los bilingües tardaron más tiempo en nombrar las imágenes en los ensayos de cambio (switch) que en los de no cambio (non-switch). Sin embargo, el "coste de cambio de idioma" fue similar para la L1 y la L2 (costes simétricos). Este efecto ha sido reportado previamente en bilingües altamente competentes (W. De Baene et al. 2015; de Bruin, Samuel, and Duñabeitia 2018; Calabria et al. 2011; Costa and Santesteban 2004; Köpke et al. 2021), lo que sugiere que el control utilizado para inhibir la interferencia entre idiomas es similar cuando la proficiencia en ambos idiomas es comparable. Este efecto fue evidente tanto en bilingües hablantes de castellano-euskera como de italiano-friulano, demostrando la robustez de la tarea y su aplicabilidad independientemente del par de idiomas empleados.

El Experimento II replicó los resultados conductuales en bilingües sanos a nivel neural. Es decir, se observó una mayor desincronización en los ensayos de cambio (switch) en comparación con los de no cambio (non-switch) en la banda de frecuencia alfa (8-13 Hz) en una ventana temporal consistente con procesos lexico-semánticos (~350-500ms), y este efecto fue similar en ambos idiomas (castellano y euskera). De hecho, los ritmos alfa han sido previamente asociados con redes inhibitorias que modulan el acceso y la recuperación de información léxico-semántica en la memoria a largo plazo (Di Bernardi Luft et al. 2018; Klimesch 2012). A nivel de fuentes, este efecto involucró una red bilateral de áreas cerebrales, incluidas regiones de lenguaje (e.g., lóbulo temporal anterior) y de control ejecutivo (e.g., áreas parietales y premotoras). Este resultado se encuentra en consonancia con estudios previos que indican que los bilingües reclutan tanto redes de lenguaje como de control cognitivo con el fín de resolver la interferencia entre idiomas (Campbell and Tyler 2018; Duffau, Moritz-Gasser, and Mandonnet 2013; Fedorenko and Thompson-Schill 2014; Friederici and Gierhan 2013; Vigneau et al. 2006; Wu et al. 2015). En líneas generales, los resultados del Experimento II sugieren que los bilingües altamente competentes implementan un mecanismo de control inhibitorio independiente del idioma involucrado (común para ambos), el cual les permite el acceso controlado a las representaciones léxico-semánticas.

En el Experimento III se comprobó que los pacientes bilingües con tumores cerebrales emplean mecanismos de neuroplasticidad (reorganización funcional), para preservar el control del lenguaje. De hecho, los pacientes exhibieron el mismo patrón en la banda de frecuencia alfa (8-13 Hz) que los participantes sanos. Esto es, mayor desincronización en los ensayos de cambio (switch) que en los de no cambio (non-switch). No obstante, a diferencia de los bilingües sanos, los pacientes mostraron adicionalmente un efecto de lenguaje. Dicho efecto también involucró modulaciones en la banda de frecuencia alfa, con mayor desincronización para la L1 que para la L2 en una ventana temporal más temprana (~150-300ms). Este último aspecto, sugiere que los procesos inhibitorios ocurrieron a otro nivel, por ejemplo, al nivel del "esquema de tarea lingüística”. Esto es, activando el idioma correcto para nombrar la imágen dependiendo del objetivo especificado por la clave contextual de color.

A nivel de fuentes, se observó el reclutamiento del giro angular y la corteza dorso-lateral prefrontal izquierda, regiones premotoras y temporales en el hemisferio derecho, y el giro frontal inferior de manera bilateral. Es interesante señalar que, además de las áreas activadas por los bilingües sanos, los pacientes mostraron el reclutamiento de una red más extensa que incluía regiones homólogas contralesionales en el hemisferio derecho. En términos generales, estos hallazgos sugieren que la afectación de áreas críticas del lenguaje por un tumor tiene un impacto diferente en la L1 y la L2 y que, para compensar posibles déficits en el procesamiento, es necesario el reclutamiento adicional de regiones de control ejecutivo y del lenguaje.

Por último, los resultados del Experimento IV sugieren que el AG y pMTG desempeñan roles diferentes en el control de procesos lingüísticos en bilingües. Específicamente, la estimulación cerebral mostró una disociación entre estas regiones y el área control (vertex), reflejada en (i) una modulación significativa en los tiempos de reacción tanto en el bloque de alternancia entre idiomas (language switching) como en los bloques de alternancia entre categorías semánticas (category switching), luego de la estimulación del AG; y (ii) una modulación específica de los tiempos de reacción durante los bloques de alternancia entre categorías semánticas luego de la estimulación del pMTG, con dicha modulación afectando principalmente el procesamiento de objetos.

El primer resultado sugiere que el AG posee un rol predominante en el control ejecutivo. No obstante, este rol es de dominio general (Wagner and Rusconi 2023) y no específico del lenguaje, dado que las modulaciones conductuales se observaron irrespectivamente del bloque testeado (tanto en la alternancia de idiomas como de categorías semánticas). Por otra parte, el segundo resultado sugiere que el pMTG se encuentra causalmente involucrado en la recuperación de representaciones semánticas (Vandenberghe et al. 1996), especialmente de aquellas referidas a objetos. Estos hallazgos sugieren que ambas regiones están involucradas en procesos de control, pero desempeñan roles diferentes.

Si bien hay limitaciones en los estudios realizados en el contexto de esta tesis, es importante señalar que estas limitaciones también pueden ser consideradas como oportunidades y puntos de partida para futuras investigaciones. En primer lugar, el tamaño de la muestra de pacientes bilingües con tumores cerebrales es relativamente pequeño, por lo que estos hallazgos deben interpretarse con precaución. Es importante destacar, que reclutar esta población específica (es decir, bilingües altamente proficientes con gliomas de bajo grado en áreas del lenguaje) es una tarea desafiante. Además, se aplicaron métodos analíticos apropiados (por ejemplo, pruebas t de Crawford) para analizar los datos a nivel de cada paciente individual, garantizando así la alta calidad científica de los resultados. No obstante, se necesitan estudios futuros con muestras más amplias para reforzar nuestras conclusiones.

Otra posible limitación, es que nuestros experimentos se centraron en bilingües con niveles similares de competencia en su L1 y L2. No está claro si el mecanismo de control y las dinámicas oscilatorias identificadas en esta población podrían extenderse a bilingües con diferentes niveles de competencia en su L1 y L2 o con perfiles inmersivos distintos. Por lo tanto, se necesitan estudios futuros que evalúen bilingües con diferentes niveles de competencia o inmersión en su L2 para arrojar luz sobre este importante tópico.

Finalmente, nuestra tarea de alternancia de idiomas se limita al entorno del laboratorio. Esto puede no reflejar con precisión las habilidades de control de idiomas en el mundo real de los bilingües. Por ejemplo, modelos recientes sobre el control de idiomas en bilingües (e.g., Hipótesis de Control

Adaptativo; Green y Abutalebi, 2013) sugieren que los mecanismos de control son flexibles y dependen del contexto en cuestión. Por lo tanto, una avenida crítica para la investigación futura es el diseño e implementación de paradigmas más ecológicos capaces de capturar el control de idiomas "en el mundo real".

En conclusión, la presente tesis doctoral ofrece una visión más completa de cómo el cerebro de los bilingües altamente competentes procesa y controla el lenguaje, incluso en situaciones clínicas complejas como la presencia de tumores cerebrales (o ante la presencia de una lesión “virtual”). Estos resultados tienen un gran potencial de aplicación clínica y pueden ser utilizados para guiar el diseño de estrategias quirúrgicas personalizadas que preserven las habilidades de control del lenguaje en pacientes bilingües durante cirugías con paciente despierto, mejorando así su calidad de vida.

ABSTRACT

Bilingual experience – the sustained contact with both a first and a second language (L1, L2) – has become an increasingly important skillset in our globalized world, as it enables individuals to communicate effectively in multiple languages and navigate diverse linguistic contexts. However, being bilingual also requires the ability to control which language to use in a given situation while avoiding interference from the non-target language. This mechanism is commonly referred to as language control and allows bilinguals to appropriately switch between their L1 and L2 depending on context requirements. Despite extensive research on the topic, a complete description of the neural dynamics (spatial, temporal, and spectral patterns) underlying this mechanism as well as its potential reorganization in the presence of brain damage, are still not fully understood.

The current doctoral thesis asked two critical questions: 1) What are the spectro-temporal and spatial signatures of bilingual language control in the neurotypical population? 2) What happens when the bilingual brain must negotiate language control in the presence of a tumor? To answer these questions, we conducted four experiments using behavioral, MEG, and TMS ("virtual-lesion" approach) measures and evaluated different populations including healthy highly proficient bilinguals and patients with left brain tumors while they performed a cue-based language switching task. Our study indicates that bilinguals with a similar level of proficiency in their L1 and L2 recruit a common inhibitory control mechanism during speech production. This mechanism is language-independent and is supported by parietal-prefrontal alpha oscillations. It allows controlled access to lexico-semantic representations in the left anterior temporal lobe and can be compensated through functional reorganization in patients with brain tumors. Furthermore, our research reveals that the AG and pMTG play distinct roles during naming in bilinguals, with the AG predominantly involved in domain-general control and the pMTG in controlled lexico-semantic retrieval across languages. These results have significant theoretical and clinical implications for our comprehension of the neural mechanisms underlying language control, as well as the preservation of language function in patients with brain damage.

List of Acronyms

Abbreviation	Explanation
ABI	Acquired Brain Injury
AG	Angular Gyrus
API	Application Programming Interface
ATL	Anterior Temporal Lobe
BA	Broca´s area
BAC	Adaptive Control Hypothesis
BEM	Boundary Element Method
BIA	Bilingual Interactive-Activation Model
CT	Computerized Tomography
DCS	Direct Cortical Stimulation
DES	Direct Electrical Stimulation
DLPFC	Dorsolateral Prefrontal Cortex
ECD	Equivalent Current Dipoles
EEG	Electroencephalography
ELAN	Early Left Anterior Negativity
ERF	Event Related Fields
ERP	Event Related Potentials
FC	Frontal Cortex
GBM	Glioblastoma multiforme
HPI	Head Position Indicators
IC	Inhibitory Control
ICA	Independent Component Analysis
IFG	Inferior Frontal Gyrus
iPC	Inferior Parietal Cortex
IPL	Inferior Parietal Lobe
ISI	Inter-Stimuli Interval
LAN	Left Anterior Negativity
LCMV	Linearly Constrained Minimum Variance
LGG	Low Grade Glioma
MEG	Magnetoencephalography

MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MTG	Middle Temporal Gyrus
NIBS	Non-Invasive Brain Stimulation
PMC	Premotor Cortex
RT	Reaction Times
SMA	Supplementary Motor Area
SMG	Supramarginal Gyrus
SQUID	Superconducting Quantum Interference Device
STG	Superior Temporal Gyrus
TBI	Traumatic Brain Injury
TC	Temporal Cortex
TFR	Time-Frequency Representations
TMS	Transcranial Magnetic Stimulation
WHO	World Health Organization
rMT	Resting Motor Threshold

CHAPTER 1: Introduction

Language is a defining feature of human cognition and culture. While the evolutionary origins of language continue to be a topic of debate among researchers (Sierpowska et al. 2022), it is evident that language skills have played a crucial role in human development and progress, from the invention of writing to the emergence of digital communication technologies (Crystal, 2000).

The creation of the European Union and the expansion of international communication networks have led to a growing interest in bilingualism, which involves sustained contact with both a first language (L1) and a second language (L2) (Paradis 2000). This increasing awareness has also influenced the scientific field (Grosjean 2010), resulting in a significant rise in the number of studies focused on bilingualism being published each year. For instance, a search for the term "bilingualism" in PubMed between 1980 and 1999 yielded only 66 scientific articles, while the same search conducted between 2000 and 2022 resulted in 9250 articles, highlighting the surge of interest in this area of research.

In daily life, bilingual speakers seem to fluently switch from one language to another while avoiding cross-language interference. Yet, to achieve this apparent effortless behavior, bilinguals need to control the languages in use. Understanding how the brain manages to communicate in one language while minimizing interference from the other language is a central topic in bilingualism research (Abutalebi and Green 2016; Green 1998). However, despite extensive research on the topic, a complete description of the neural dynamics (spatial, temporal, and spectral patterns) underlying this mechanism as well as its potential reorganization in the presence of brain damage, are still not fully understood.

The current doctoral thesis addresses two main questions: 1) What are the spectro-temporal and spatial signatures of bilingual language control in the neurotypical population? 2) What happens when the bilingual brain must negotiate language control in the presence of a tumor?

Understanding the neural and cognitive mechanisms of language control has important implications not only for advancing our understanding of bilingualism but also for its potential practical applications in clinical contexts (Abutalebi and Green 2016).

1.1 Whom do we call bilinguals?

Bilingualism was thought to be a *rara avis* but that is no longer the case; with approximately 65% of the world's population being bilingual and constantly growing (EuroStat 2016). Despite this widespread phenomenon, there is no unique definition of bilingualism. For instance, Bloomfield (1933) defined bilinguals as individuals who exhibit a level of mastery in two languages that is comparable to that of a native speaker (Bloomfield 1933). Later on, Haugen (1953) introduced the concept of bilingualism as the capacity to produce coherent and meaningful utterances in a second language (Haugen 1953). For the Canadian linguist William F. Mackey what defines bilingualism is instead the ability to use two languages interchangeably, regardless of how often they are used (Mackey 1962). French scientist François Grosjean, conversely, characterizes bilinguals as individuals who use both languages in their every-day lives (Grosjean 1989). Furthermore, Grosjean (1989) argues that bilinguals should not be viewed as the sum of two separate monolinguals, since the fusion of multiple linguistic competencies within an individual creates a distinct and comprehensive linguistic entity.

Nevertheless, despite the absence of a universally accepted definition of bilingualism, some experience-based factors allow us to establish some tentative classifications. One of these factors is the age of acquisition (AoA). Depending on AoA, three subgroups can be considered: (i) early simultaneous (both languages acquired before the age of 3), (ii) early sequential (both languages are acquired early, but one of the languages is acquired before the other), and (iii) late sequential (an adult learns a language later in life) (Genesee, Nicoladis, and Paradis 1995; Johnson and Newport 1991). Another critical factor is the level of proficiency. According to this aspect, bilinguals can be considered as (i) balanced (both languages are at high proficiency) or (ii) unbalanced (one of the languages is stronger than the other) (Grosjean 1998).

Classically, these classifications were thought to differentiate between bilinguals and monolinguals. However, nowadays, bilingualism is viewed as a continuous variable rather than a categorical one (Luk and Bialystok 2013). Overall, understanding the impact of experience-based factors on bilingualism and the potential limitations of traditional classifications in capturing individual differences in bilingual experience is an important area of study in today's world. In other words, as the number of bilingual individuals continues to grow, it is crucial to have a more nuanced understanding of the complexity and diversity of bilingualism.

1.2 What is language control?

One of the key questions in the study of bilingualism is how individuals manage to communicate in the target language while minimizing interference from the non-target language. Language control refers to a collection of cognitive mechanisms (i.e., conflict monitoring, response selection, and response inhibition) that enable bilinguals to achieve this endeavor (Abutalebi and Green 2007, 2008; Green 1998; Kroll and Bialystok 2013). However, the nature of this mechanism remains a topic of debate (Gray and Kiran 2016).

One of the most common paradigms used to investigate language control is the language switching task. In this task, bilinguals are asked to name a series of pictures or words in their first language (L1) or second language (L2) depending on a cue. For example, a green cue might indicate the use of the L1, and a red cue the use of the L2. The task requires bilinguals to switch between languages and suppress interference from the non-target language, thereby providing a measure of language control ability. Bilingual switching studies concur that for trials in which participants must switch between languages—compared to trials in which participants stay in the same language— the effort is greater, leading to longer RTs and higher error rates. This finding is very robust and has been replicated widely with multilingual individuals from many different linguistic backgrounds (W. De Baene et al. 2015; Blanco-Elorrieta and Pylkkänen 2017; Bobb and Wodniecka 2013; Branzi et al. 2016; Declerck and Kormos 2012; Hervais-Adelman, Pefkou, and Golestani 2014; Philipp, Gade, and Koch 2007). However, this pattern of being slower to switch to a more challenging task also replicates across a whole range of tasks that hold no relation to language processing (Cherkasova et al. 2002; Ellefson, Shapiro, and Chater 2006; Koch Iring 2010; Lemaire and Lecacheur 2010; Wylie and Allport 2000), underscoring parallelisms between linguistic and non-linguistic control.

These findings had led to a sustained debate on whether control mechanisms involved in managing interference between languages are domain-general (i.e., meaning that they are not specific to language processing) or domain-specific (i.e., namely, restricted to language processing (Liu et al. 2014)). While some previous studies have found evidence for the existence of a partial or fully independent mechanism devoted to language control (Calabria et al. 2011; Declerck and Philipp 2015; Jylkkä et al. 2018), most current views suggest that both types of mechanisms might be involved (Campbell and Tyler 2018; Duffau et al. 2013; Fedorenko and Thompson-Schill 2014; Friederici and Gierhan 2013; Vigneau et al. 2006; Wu et al. 2015).

1.2.1 Neural basis of language control: from neurons to brain rhythms

The brain's ability to process and integrate information in real-time is crucial for our everyday neurocognitive activities, including language comprehension and production. This process involves the communication between neurons which entails the conversion of chemical signals into electrical ones. Briefly, each neuron consists of three main components: the soma, the dendrites, and the axon. The soma is crucial for integrating and processing signals from other neurons, while the dendrites serve to receive these signals through synapses. The axon, on the other hand, is responsible for transmitting signals to other neurons. The process of neuronal communication involves changes in the membrane potential of the postsynaptic neuron, which ultimately alters its electrical properties. An action potential is initiated when a neuron receives a signal from other neurons. This signal induces a change in the electrical charge of the cell membrane, causing a depolarization of the membrane potential. If the depolarization exceeds a certain threshold, voltage-gated ion channels in the membrane are activated, allowing positively charged ions such as sodium (Na+) to enter the cell, causing further depolarization. When an action potential reaches the axon terminal of the presynaptic neuron, it triggers the release of neurotransmitters into the synaptic cleft, a narrow space between the two cells. These neurotransmitters then bind to receptors on the postsynaptic neuron, inducing changes in its membrane potential that can either excite or inhibit the neuron. This mechanism ultimately determines whether the postsynaptic neuron will fire an action potential and continue the signal transmission. However, the electrical signals generated by individual neurons are typically undetectable unless directly recorded using specialized techniques (e.g., ECoG). In contrast, the combined activity of thousands of neurons can be measured non-invasively by placing sensors on the scalp. To achieve this some criteria must be met. For instance, pools of neurons should fire together and be spatially aligned. Furthermore, these neurons must be of a particular type. Pyramidal neurons located in the cerebral cortex have a unique anatomical structure with a long apical dendrite perpendicular to the cortical surface. The firing of these neurons produces a “dipole moment” (i.e., separation of positive and negative charges) which reflects the synchronous activity of large populations of neurons in the brain.

This synchronous activity can be detected at the scalp level with the appropriate techniques such as electroencephalography (EEG) and magnetoencephalography (MEG). Although they both provide direct information about the neural activity, they differ in the way they capture the signal.

EEG measures the electrical activity of the brain by recording the voltage changes on the scalp, while MEG captures the magnetic fields generated by this electrical activity.

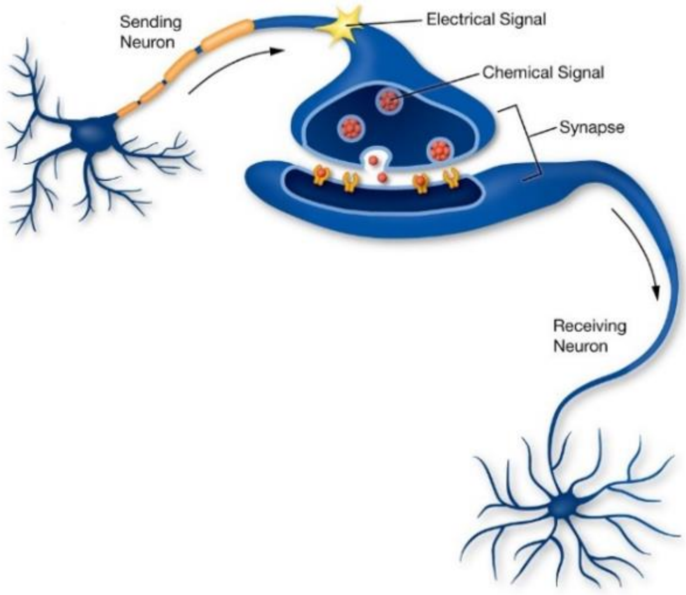


Figure 1. Neural communication. The transmission of information from one neuron to another occurs across a small gap known as a synapse. At the synapse, electrical signals are converted into chemical signals, which traverse the gap and are then converted back into electrical signals to continue the transmission of information between neurons. Picture adapted from **https://learn.genetics.utah.edu/content/neuroscience/neurons**.

The development of EEG and MEG started as early as the end of 19 century. The first EEG signal was recorded from a human subject in 1924 by Hans Berger, but the magnetic fields in the brain were only recorded 24 years later (Cohen 1968) The advantages of these techniques are that they provide a direct measure of neural activity, they are not invasive and safe for participants (e.g., MEG can even be used on unborn babies (Sheridana et al. 2010) and they can track brain activity with excellent temporal resolution (i.e., at the millisecond level). This aspect becomes critical when considering language processing which occurs on the sub-second time scale (e.g., speech has a production rate of 3-5 words per second).

By studying the patterns of dipole moment activity in different brain regions and under different experimental conditions, researchers can gain insights into the neural mechanisms underlying cognition and behavior. To isolate and study the neural activity associated with language processing, researchers often employ linguistic tasks (e.g., reading, picture-naming) and simultaneously record the participants' brain activity using EEG/MEG. One popular method is to measure event-related potentials (ERPs). ERPs are voltage fluctuations that result from averaging segments of brain activity associated with the presentation of specific events (stimulus or response) and reflect cognitive processes with a specific polarity, latency, and topography (Luck 2005). Researchers have identified several language-related components based on these characteristics. For instance, the N400 is a negative deflection in the ERP waveform that typically peaks around 400 milliseconds after the presentation of a meaningful stimulus (such as a word). The N400 is thought to reflect semantic processing, with larger N400 amplitudes being observed for words that are semantically anomalous or incongruous within the context of a sentence (Kutas and Federmeier 2011). The P600 component is a positive deflection in the ERP waveform that typically peaks around 600 milliseconds after the presentation of a stimulus and is thought to reflect syntactic processing; with larger P600 amplitudes being observed for sentences that contain grammatical violations or errors (Frisch et al. 2002).

However, classical time-locked ERP/ERF analysis is blind to information not phase-locked to the stimuli, resulting in less sensitivity when tapping into ongoing neurocognitive dynamics associated with language processing (Braunstein et al. 2012; Mouraux and Iannetti 2008).

Time-frequency analysis, on the other hand, is a powerful technique used to analyze M/EEG signals and provides a way to investigate the spectro-temporal dynamics of brain activity. This method involves decomposing the M/EEG signal into its constituent oscillatory components, which allows researchers to examine how different frequency bands contribute to brain activity over time. Indeed, oscillatory activity is thought to play a critical role in neural communication and to reflect distinct cognitive operations at different frequency bands (Fries P 2005), providing a fine-grained characterization of neurophysiological mechanisms supporting cognition. Time-frequency analysis offers a more nuanced characterization of brain activity compared to traditional ERP/ERF analyses, as it allows for the detection of transient changes in oscillatory activity that may be important for understanding cognitive processes (for a recent review see (Rothman et al. 2022)).

When considering bilingual language control, previous findings mainly point to the involvement of two neural oscillations: theta (4–7 Hz) and alpha (8–13 Hz) rhythms (Tao et al. 2021). See Table 1 for a summary of the studies showing the effects associated with these brain rhythms.

On the one hand, theta power increases have been reported for L2 as compared to L1 switching during speech production in low-proficient Chinese-English bilinguals with high inhibitory control abilities, possibly indexing cross-language interference at the lexical selection level (Liu et al. 2015). Another study on word production in unbalanced Dutch-English bilinguals (Piai and Zheng 2019), found theta power increases after participants selected the wrong language for speaking during cued language switching, reflecting a role for theta in the monitoring of speech errors. Similarly, in non-linguistic tasks in which participants have to deal with conflicting information (e.g., Go-no go, Flanker task), theta power increases have been observed in incongruous as compared to congruous trials (Cohen and Donner 2013; Nigbur, Ivanova, and Stürmer 2011; Van Steenbergen, Band, and Hommel 2012), thus supporting its broader involvement in executive control (e.g., conflict monitoring) under situations of increased cognitive demands.

On the other hand, oscillatory activity in the alpha frequency band (8-13 Hz) has been consistently linked to functional inhibition (Jensen and Mazaheri 2010; Klimesch 2012; Klimesch, Sauseng, and Hanslmayr 2007). Under this view, alpha is considered a general mechanism that subserves various cognitive processes that use inhibitory control in tasks requiring interference suppression. When considering language control, bilinguals tend to exhibit overall higher alpha power than monolinguals (Bice, Yamasaki, and Prat 2020), with this power correlating with L1 and L2 experience-related measures. Furthermore, alpha oscillations have been linked to lexico-semantic access in highly proficient bilinguals (Geng et al. 2022) and are thought to shape inhibition in semantic association networks, allowing the controlled retrieval of information from long-term memory (Di Bernardi Luft et al. 2018; Klimesch 2012).

Table 1. Time-frequency components and their function in language processing

Frequency band	Function associated	Publications
Theta (4-7Hz)	Monitoring of speech errors Inhibition of cross-language interference at the lexical selection level	(Piai and Zheng 2019) (Liu et al., 2015)
Alpha (8-13Hz)	Functional inhibition	(Jensen and Mazaheri 2010; Klimesch 2012; Klimesch et al. 2007; Piai, Klaus, and Rossetto 2020; Piai, Roelofs, and van der Meij 2012)Timofeeva et al., submitted)
	Lexico-semantic access	(Geng et al. 2022)
	Retrieval of information from long-term memory	(Di Bernardi Luft et al. 2018; Klimesch 2012)

Altogether, these findings suggest that theta and alpha frequency bands might play a key role in bilingual language control. Nevertheless, only a few studies have attempted to investigate the oscillatory dynamics subserving this process during speech production (Liu et al. 2015). Furthermore, to the best of our knowledge, no study has approached this topic while considering highly proficient bilinguals.

1.2.2 Language models

The foundations of modern cognitive neuroscience were laid in the 1860s through the pioneering work of physicians Paul Broca and Carl Wernicke. Their discoveries of specific brain regions responsible for speech production (see Fig. 2) and language comprehension, respectively; offered for the first time empirical evidence for associations between specific brain areas and language processing (e.g., behavioral-structural correlations).

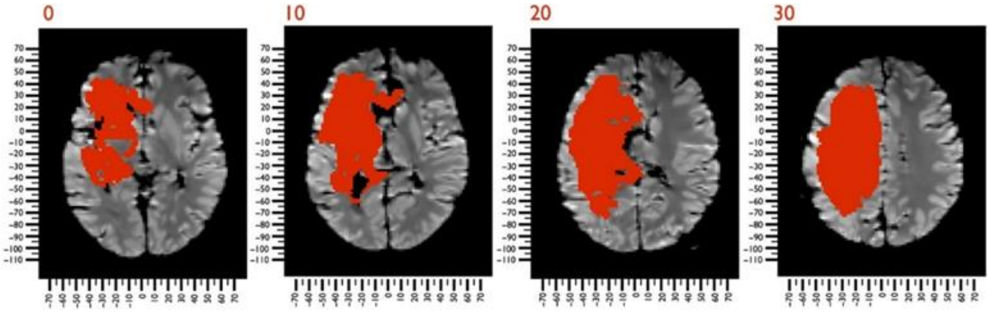


Figure 2. T1-weighted MRI images of Broca's patient Leborgne. At the time of the discovery, MRI did not exist and these findings were based on postmortem observations. Later on, an MRI was performed revealing that the lesion mainly affected insular and premotor cortices and perisylvian white matter fibers (in red). Picture adapted from (Thiebaut De Schotten et al. 2015).

According to Wernicke, there were two distinct areas in the brain involved in language processing: the sensory speech center (also known as Wernicke's area) and the motor speech center (also known as Broca's area). Wernicke believed that these two areas were connected and communicated with each other through neural links. He shared this view with another influential researcher, Ludwig Lichteim, and together they created the first simplified model of the neurology of language in 1885 (Lichteim 1885; Wernicke 1969). A century later, this model was further improved and popularized by Norman Geschwind (Geschwind 1970, 1971) in the form of what is often called the Wernicke-Lichtheim-Geschwind (WLG) or simply the classical model (Figure 3), consisting of Wernicke's area (in the superior temporal gyrus), Broca's area (in the inferior frontal gyrus), and the arcuate fasciculus, a white matter tract of fibers connecting both regions. The WLG model led to the creation of the *localizationist* view. While some aspects of this model have been updated or refined with newer research, it had a significant impact on our understanding of the brain basis of language.

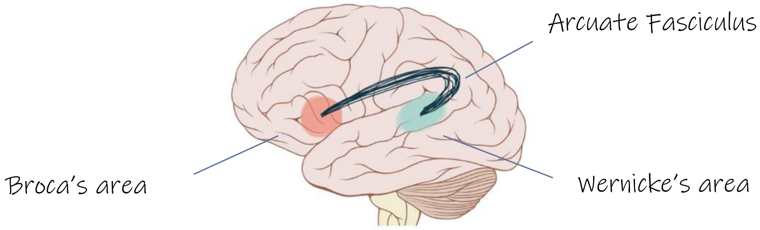


Figure 3. Classical Wernicke-Lichtheim-Geschwind model

More recent developments in brain mapping techniques, such as functional neuroimaging and direct electrical stimulation during awake surgery for tumor resection, have brought about a fundamental shift in how we view neural architecture. It is now widely recognized that the brain is structured as complex distributed networks with high potential for plasticity (e.g., connectomal account of neural processing), meaning that brain regions that were previously deemed "critical" under the localizationist approach (e.g., Broca's area or Wernicke's area) can be removed without any functional deficits (Duffau 2018b).

Between 2000 and 2007, David Poeppel and Gregory Hickok developed the Dual Stream Model (Hickok and Poeppel 2000, 2004, 2007). This model aimed to explain how the human brain experiences and perceives speech stimuli. It differs from previous theories proposed by Broca and Wernicke, which had a more modular and localizing approach. The Hickok-Poeppel theory instead proposes the existence of two processing pathways for speech: the dorsal stream and the ventral stream. The dorsal stream is responsible for mapping sound to articulation, while the ventral stream is responsible for mapping sound to meaning. This model suggests that both pathways work together in parallel and interact with each other, leading to a more integrated and distributed network for language processing in the brain. However, as stated before, this model is focused on language comprehension, leaving unanswered the question of how speakers produce speech.

Among existing models of language production (Butterworth n.d.; Caramazza 1997; Dell 1986; Garrett MF 1980; Stemberger 1985) there is an acceptable agreement on the existence of different processing levels, including meaning, form, and articulation.

In this context, the Levelt model of language production, proposed by Willem Levelt (Levelt 1989), is a widely recognized framework for understanding how speakers produce language. According to this model, language production involves three stages: conceptualization, formulation, and articulation. During conceptualization, speakers generate the message they want to convey. In the formulation stage, this message is translated into a linguistic representation, which involves selecting appropriate words, grammatical structures, and syntactic rules. Finally, during the articulation stage, the linguistic representation is transformed into motor commands that allow the speaker to produce speech. Briefly, when a speaker wants to produce a word, the appropriate lemma is selected from the mental lexicon and then transformed into a phonological form that can be articulated. This model also emphasizes the dynamic and interactive nature of these processes and acknowledges the role of feedback and monitoring mechanisms in language production. This model was revisited later on (Indefrey 2011; Indefrey and Levelt 2004) including a temporal and spatial description of word production based on findings derived from neuroimaging and neurophysiological data (see Figure 4).

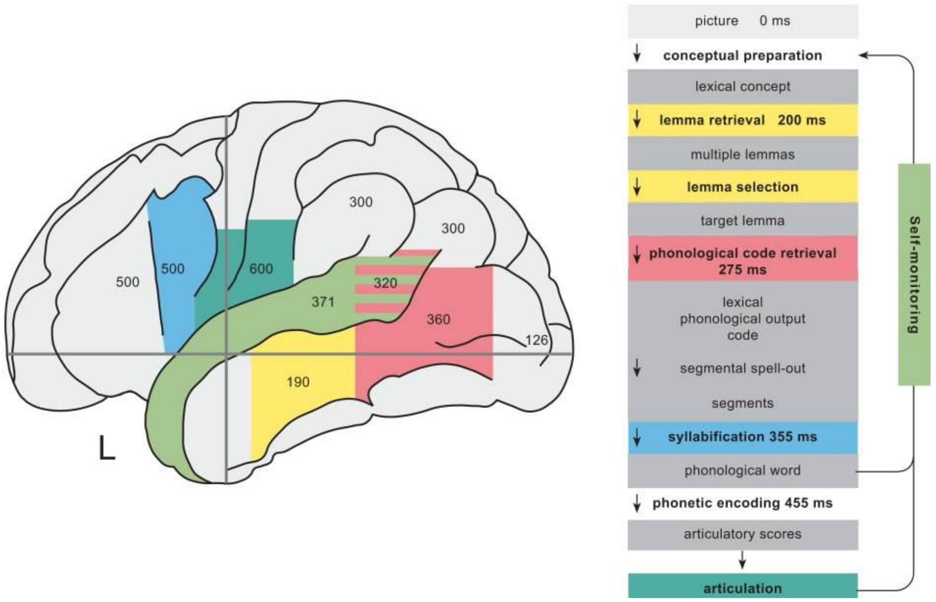


Figure 4. Left column: schematic representation of the activation time course of brain areas involved in word production. Colors indicate relationships between brain regions and functional processes. Numbers within regions indicate median peak activation time estimates (in milliseconds) after picture onset in picture naming. Adapted from (Indefrey 2011).

1.2.3 Cognitive models of bilingual language control during speech production

Bilingualism research and related models, initially relied on monolingual theories, until bilingualism researchers challenged and criticized the notion that bilingualism was just an extension of monolingualism. Indeed, as Grosjean (1989) highlighted, bilinguals are not merely the sum of two separate monolingual individuals with two distinct languages. The fusion of multiple linguistic competencies within an individual creates a distinct and comprehensive linguistic entity. As a consequence, numerous psycholinguistic models of bilingual language representation and processing were formulated and developed, which still hold significant influence today.

Briefly, language control models can be divided into two groups: those that mainly explain language control in comprehension (e.g., the Bilingual Interactive Activation Model [BIA] proposed by Dijkstra & Van Heuven in 1998, and later extensions such as the BIA+, Dijkstra and van Heuven, 2002 and the BIA-d, Grainger et al., 2010) and those that rely on language production (for a review see (Declerck and Philipp 2015). The scope of this thesis is limited to language production; therefore, only models that address this particular aspect will be considered.

The Revised Hierarchical Model (RHM) is a psycholinguistic model of bilingual word production, proposed to account for performance in translation production (Kroll and Stewart 1994). The RHM posits that bilinguals have two separate and independent lexical systems, one for each language and a shared semantic system. The L1 lexicon is assumed to be larger than the L2 lexicon because bilinguals generally have a higher vocabulary in their native language. In less proficient bilinguals, concepts in the L2 would be accessed through the L1 via translation. The model proposes asymmetric access to meaning in their two languages. However, with greater proficiency, it would be possible to access concepts directly through the L2. Even if appealing, the two-lexicons view has been challenged by a number of studies (e.g., see (Hernandez, Martinez, and Kohnert 2000)) and this model, at least in its original form, is now considered obsolete (Kroll et al. 2010).

The Inhibitory Control Model (IC) is one of the most influential and dominant models of bilingual speech production. It was proposed by Green in 1998 and later refined by Abutalebi and Green in 2007. The model is inspired by the RHM and Levelt's models, but it is unique in its focus on inhibition as a mechanism that supports bilingual control.

According to the IC model, switching between two languages during speech production incurs a cost: different language schemas are simultaneously active and to produce output in the intended language, the non-intended one must be inhibited. However, there will be also a cost in overcoming inhibition within the system. Because inhibition is reactive, the more active a language is, the more it will be inhibited. As a result, switching costs are predicted to be asymmetric, with greater costs for switching to the more suppressed language. This is particularly relevant for unbalanced bilinguals, whose dominant language (L1) is more likely to be subject to inhibition. Therefore, switching to L1 is expected to take longer (Meuter and Allport 1999). Conversely, for bilinguals showing similar proficiency in both languages, the IC model predicts that the switching cost should be symmetric, given that the amount of inhibition deployed to control for activation across languages should be equivalent. This prediction is indeed supported by behavioral data from highly proficient bilinguals showing symmetric switch costs when alternating between languages during picture-naming tasks in mixed-language contexts (W. De Baene et al. 2015; de Bruin et al. 2018;

Calabria et al. 2011; Costa and Santesteban 2004; Costa, Santesteban, and Ivanova 2006; Köpke et al. 2021).

More recently, a third model has been proposed, which can be roughly considered an extension of the IC model: the Adaptive control hypothesis (ACH, (Green and Abutalebi 2013)). The ACH proposes that bilingual language control mechanisms are flexible and context-dependent, allowing bilinguals to efficiently navigate between languages depending on the demands of the situation (Green and Abutalebi 2013). Specifically, this model proposes that language switching can be viewed in three contexts requiring differing degrees of demands: (i) single language context (i.e., L1 and L2 are used in different environments, for instance, the L1 at home and the L2 at school; and thus language switching is infrequent), (ii) dual language context (i.e., L1 and L2 are used within the same environment and thus language switching is frequent) and (iii) dense code-switching context (i.e., speakers mix their L1 and L2 in the course of single utterances; especially in multilingual communities where mixing is common). According to this theory, when bilingual individuals encounter high levels of language conflict (e.g., in dual language contexts), they rely more heavily on domain-general cognitive control mechanisms to suppress the non-target language and enhance language-specific control mechanisms to facilitate the target language. On the other hand, when the level of conflict is low, bilingual individuals rely more on domain-specific language control mechanisms, which are more efficient and less demanding on cognitive resources.

The bilingual must constantly monitor and adjust to the context using salient cues. To achieve this goal, the authors suggest that a set of processes needs to be accomplished: goal maintenance, conflict monitoring, interference suppression, salient cue detection, selective response inhibition, task engagement and disengagement, and opportunistic planning. The different contexts impact these processes. For instance, bilinguals in single-language contexts will show small changes in goal maintenance and conflict monitoring, while those aspects will be strongly affected in dual language-contexts.

1.2.4 Neural networks involved in bilingual language control during speech production

Most of what we know today about the neural basis of bilingual language control during production is primarily through studies using language switching during picture-naming tasks (Tao et al. 2021).

A large number of neuroimaging studies (Abutalebi 2008; W. De Baene et al. 2015; Blanco-Elorrieta and Pylkkänen 2016; Branzi et al. 2016; De Bruin et al. 2014; Fan et al. 2016; Garbin G et al. 2011; Guo et al. 2011; Hernandez 2009; Hernandez et al. 2001, 2000; Lei, Akama, and Murphy 2014; Ma et al. 2014; Price, Green, and Von Studnitz 1999; Sierpowska et al. 2013, 2018; Wang et al. 2007, 2009; Zhang, Gan, and Wang 2014a, 2014b; Zou et al. 2012) have consistently shown the involvement of a frontoparietal-subcortical network in bilingual language control, including domain-general cognitive control areas (shown in yellow in Fig. 5) such as the dorsolateral prefrontal cortex (dlPFC), pre-supplementary motor area (pre-SMA), anterior cingulate cortex (ACC), the caudate nucleus of the basal ganglia, and the inferior parietal cortices (IPC); language-related areas such as superior (STG) and the middle temporal (MTG) gyri (in orange) and mixed areas such as the inferior frontal gyrus (IFG). It has been suggested (De Frutos-Lucas et al. 2020; Grant, Fang, and Li 2015) that in low proficient bilinguals or during the initial stages of learning a second language, the engagement of domain-general control areas (e.g., dlPFC) may be more critical to effectively manage both languages. As proficiency and exposure in the L2 increase, bilingual language control may shift towards more language-specific processing, especially when it comes to semantic processing.

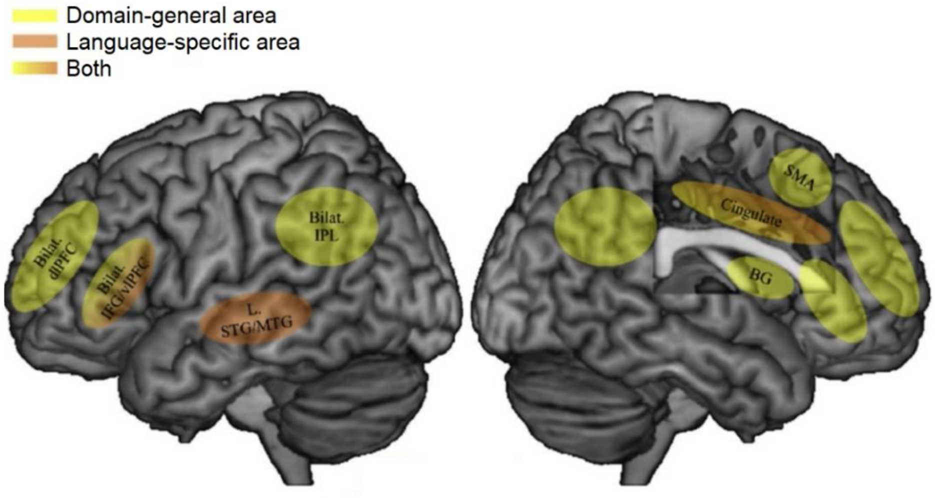


Figure 5. Overview of neural responses during bilingual language control (adapted from (Tao et al. 2021)).

1.3 What can brain tumor patients teach us about language control in the bilingual brain?

Brain tumor patients can offer us unique insights into the neural mechanisms involved in language control and the brain's capacity to reorganize linguistic functions in the presence of a lesion. In the case of bilingual individuals, a developing brain tumor can affect one or both languages and the ability to switch between them. By investigating this population, we can gain valuable insights into the neural underpinnings of language control and its plasticity.

1.3.1 Brain tumors and their classification

With more than 3 million new cases and 1.7 million deaths each year, cancer is considered by the European Commission as one of the biggest killers of the 21st century. Gliomas are the most common primary brain tumors affecting people at a young age (i.e., 4th decade of life). Based on their malignant behavior and progression rate, they can be classified as WHO grades I–IV (see table 2).

Table 2. WHO brain tumor classification

Grade		Characteristics	Tumor types
Low grade	WHO Grade 1	○ Least malignant (benign) ○ Possibly curable via surgery alone ○ Non-infiltrative ○ Long-term survival ○ Slow growing	○ Pilocytic astrocytoma ○ Craniopharyngioma ○ Gangliocytoma ○ Ganglioglioma
	WHO Grade 2	○ Relatively slow growing ○ Somewhat infiltrative ○ May recur as a higher grade	○ "Diffuse" Astrocytoma ○ Pineocytoma ○ Pure oligodendroglioma
High grade	WHO Grade 3	○ Malignant ○ Infiltrative ○ Tend to recur as higher grade	○ Anaplastic astrocytoma ○ Anaplastic ependymoma ○ Anaplastic oligodendroglioma
	WHO Grade 4	○ Most malignant ○ Raid growth, aggressive ○ Widely infiltrative ○ Rapid recurrence ○ Necrosis prone	○ Glioblastoma multiforme (GBM) ○ Pineoblastoma ○ Medulloblastoma ○ Ependymoblastoma

Low-grade gliomas (LGGs) are a type of brain tumor that develop when nerve tissue cells grow and divide uncontrollably. These tumors are known for their slow growth rate (around 4 mm/year) which allows the brain to adapt and reorganize gradually through different compensatory mechanisms. These mechanisms involve the relocation of functions from damaged areas to healthy ones (Herbet et al. 2016). LGGs are often diagnosed based on symptoms such as new-onset epilepsy, headaches, motor deficits, nausea, and dizziness (Ghandour et al. 2021; Peeters et al. 2019).

The gold standard procedure to treat LGGs is a partial or complete resection through an awake craniotomy (AC). In the last decades, AC and functional mapping with Direct Electrical Stimulation (DES) have been extended to tumor resection in eloquent areas giving optimal results (Bulsara, Johnson, and Villavicencio 2005) The main purpose of brain surgery is to optimize the extent of resection while avoiding post-surgery sequelae, thus improving the patient's quality of life. On average, patients have a longer survival rate post-surgery when a supra-maximal resection is achieved (Duffau 2016; Zigiotto et al. 2020). During AC, the patient goes under anesthesia until neurosurgeons reach the tumor and then awaken. Patients are asked to perform a series of cognitive tasks meant to map the eloquent areas surrounding the tumor to better establish which tissue could be removed or should be preserved based on functional boundaries. This type of procedure reduces the risks of post-operative neurological deficits and is primarily used in cases when language, motor, or visual areas are affected by the tumor (Dadario et al. 2021). To map functionality, neurosurgeons combine DES (i.e., a bipolar electrode to stimulate different cortical and subcortical areas) with cognitive tasks (i.e., naming objects, language switching, etc.), which are *a priori* selected depending on tumor location. DES is a powerful method for studying the relationship between structure and function by creating a “temporary lesion” in a given area through electrical stimulation, allowing neurosurgeons to observe changes in behavior in real-time. This technique provides high spatial resolution and is used to gain insight into the function of various cortical and subcortical regions during AC. Indeed, thanks to the implementation of this technique, tumors considered inoperable became operable with an increased survival rate and decreased postoperative cognitive deficits (Duffau 2018a).

Recent evidence suggests that the presence of LGG in language-related areas induces their functional reorganization (Yuan et al. 2020; Zhang et al. 2018). Many factors can affect this functional reshaping, including tumor grade (Taphoorn and Klein 2004; Yuan et al. 2020), patient´s age (Zhang et al. 2018), tumor location (Duffau et al. 2003; Ghumman et al. 2016; Harris et al. 2014; Maesawa et al. 2015; Zhang et al. 2016), sex (Kuo et al. 2001) and genetics (Pearson-Fuhrhop and Cramer 2010).

Interestingly, when the damage affects white matter tracts, functional compensation seems to be reduced or completely absent, as reported in patients with diffuse LGGs (Herbet et al. 2014; Ius et al. 2011), stroke (He et al. 2007) and other pathologies (Cristofori et al. 2015; Fagerholm et al. 2015; Genova et al. 2014; Herbet, Latorre, and Duffau 2015; Sharp, Scott, and Leech 2014).

In particular, the use of DES (Lucas, McKhann, and Ojemann 2004; Roux et al. 2004; Walker et al. 2004) during awake craniotomy of bilingual patients, suggests that although both languages share gross anatomical areas (in frontal, parietal, and temporal regions), there are also microanatomical systems and subcortical tracts (Bello et al. 2006), which respond specifically to one language or another (Paradis 2004). Thus, the most important conclusion that emerges at the clinical level from these results is that, during the AC, all the languages a patient speaks should be mapped (Giussani et al. 2007).

Based on DES evidence during intra-operative mapping and previous fMRI findings, Moritz-Gasser and Duffau (S Moritz-Gasser and Duffau 2009) proposed an anatomo-functional model of language control. In this model, language switching engages two networks: an executive control system spanning ACC, SMA, and DLPFC regions, and a cortico-subcortical language system. This latter system might control a specific language sub-circuit that involves three main epicenters: (1) the left IFG, (2) the inferior parietal lobe (SMG, AG); and (3) the posterior superior temporal–fusiform areas, which would be interconnected by the superior longitudinal fasciculus (SLF).

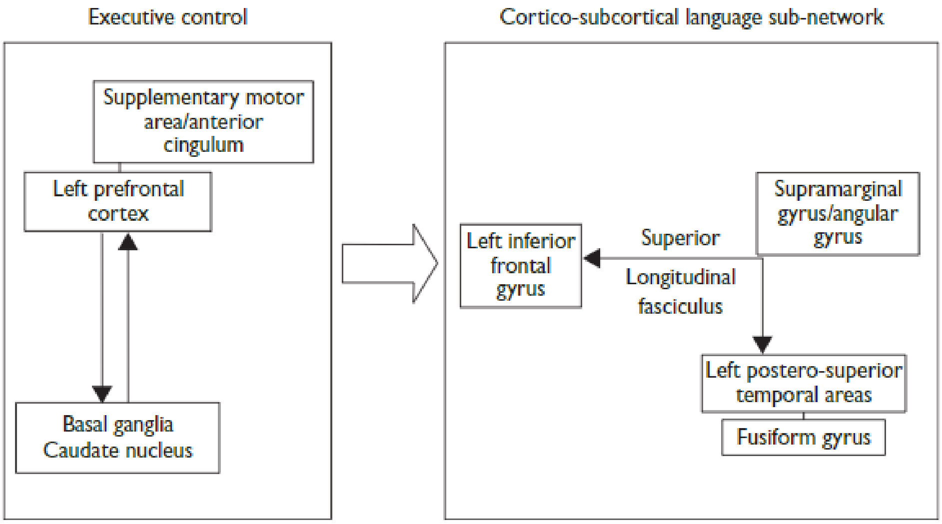


Figure 6. Model of distributed neural network of bilingual language control proposed by Duffau and Moritz-Gasser based on patients' data. Figure adapted from (S Moritz-Gasser and Duffau 2009)

Later on, in 2013, the authors revisited this model integrating findings from picture-naming in patients with LGGs, which further supported the interplay of the language network with the executive control system. Overall, based on DES data, the authors suggest that language and executive control are tightly intertwined and cannot be separated from each other. Nevertheless, DES research on bilingual language control using language-switching tasks is limited, with all of the existing findings being summarized in Table 3.

Table 3. Overview of brain areas affected by LGGs and type of errors elicited by DES during intra-operative mapping using a language switching task.

Area	Type of errors	Study
IFG	Language switch errors in both directions Pathological switching L1 to L2	(Sierpowska et al. 2018; Wang et al. 2013) (Kho et al. 2007)
MFG	L2 to L1 switch error, L1 to L2, and L3 to L2 involuntary switching	(Lubrano et al. 2012; Sierpowska et al. 2013, 2018; Wang et al. 2013)
DLPFC	Involuntary language switching	(Lubrano et al. 2012)
SFG	L1 to L2 Involuntary switching	(Wang et al. 2013)
ACC/SMA	L1 to L2 Involuntary switching	(Wang et al. 2013)
PTA	Language switch error	(Moritz-Gasser and Duffau 2009)
SLF	Language switch error	(Moritz-Gasser and Duffau 2009)
STG	Involuntary switching L1 to L2	(Moritz-Gasser and Duffau 2009)

1.3.2 Neuroplasticity

Neuroplasticity refers to the brain´s ability to modify its structure and function in response to internal and external factors (Duffau 2005). Up until the 70', researchers believed in the idea that plasticity mostly occurred in critical periods of development (i.e., childhood and adolescence), and that adults were not capable of creating new connections or modifying existing ones (Owji and Shoja 2020). However, with the advent of neuroimaging techniques, researchers have discovered that neuroplasticity continues throughout adulthood (Draganski and May 2008).

Neuroplasticity in the damaged brain has been primarily studied in stroke patients. However, the sudden and acute nature of this type of lesion only allows for studying compensatory mechanisms once core damage has occurred (i.e., post-stroke plasticity). Furthermore, in these cases, even small lesions can lead to irreversible deficits and poor functional recovery, possibly due to the time-course of the damage, in which tissue is destroyed instantaneously, not enabling the reallocation of the knowledge that was previously encoded (Keidel, Welbourne, and Lambon Ralph 2010). As recently suggested by some authors, the stroke seems to represent a limited model to study neuroplasticity and functional compensation (Duffau 2005). An interesting and poorly studied population comprises patients harboring LGGs (Kong, Gibb, and Tate 2016). Due to their slow growth, these tumors destroy the cortex gradually, allowing the brain to adapt and transfer linguistic functions progressively without severe neurological and behavioral deficits (DeAngelis 2001). In other words, unlike a stroke, LGG damage takes place continuously but slowly, allowing other brain regions to assume the role previously played by the damaged tissue.

Evidence shows the existence of diverse neuroplasticity mechanisms in the presence of LGGs including the engagement of peritumoral regions as local compensation (Deverdun et al. 2020; Duffau et al. 2003; Lizarazu et al. 2020) and the recruitment of remote ipsilesional and/or contra-lesional areas, such as homotopic reorganization of gray matter volume (Almairac, Duffau, and Herbet 2018) or activation patterns (Desmurget, Bonnetblanc, and Duffau 2007). Due to the differences between brain function and structure from one individual to another, neuroplasticity mechanisms also show variability (Dadario et al. 2021).

Overall, evidence from studies using DES in patients with LGGs opens a new window into neuroplasticity mechanisms. However, this technique has some limitations. One of the main issues is that, as it requires an invasive procedure and only can be used in certain clinical populations, the sample size is typically small. Additionally, the assessment of behavioral changes is often restricted to the duration of the surgery, making the range of behavioral assessments limited (Duffau, 2015). These limitations can be overcome with Transcranial Magnetic Stimulation (TMS), a non-invasive brain stimulation technique that can induce short-term (i.e., transient) plasticity in the brain and can be applied to the neurotypical population.

1.4 Simulating brain damage through a "virtual lesion approach"

In 1831, Michael Faraday discovered the principle of electromagnetic induction that became the basis for TMS development. TMS uses magnetic fields to modulate brain excitability, offering the unique possibility to (i) transiently modulate neural activity in regions of interest and (ii) measure the consequent changes in observable behavioral responses, allowing to establish causal relationships between cortical structure and cognitive functions (Bergmann and Hartwigsen 2021).

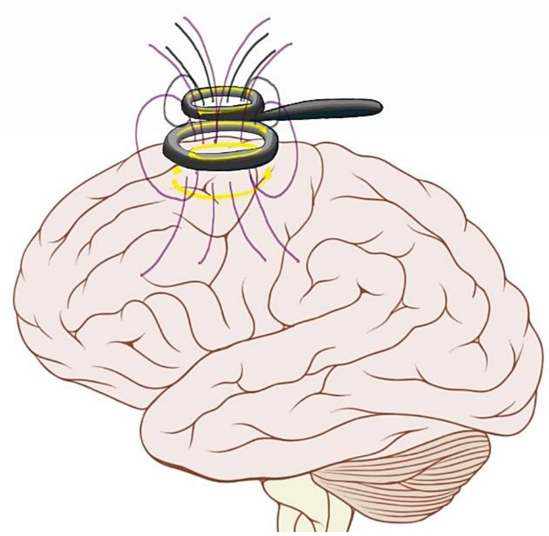


Figure 7. TMS stimulation coil applied to the brain surface

As shown in Figure 7, a coil of wire encased in plastic is held close to the participant's head (either by the experimenter or by a mechanical arm). When current is allowed to pulse through the coil by discharging a capacitor, a rapidly changing current flows through its windings. This, in turn, produces a magnetic field oriented orthogonally to the plane of the coil, which passes through the skin and skull, inducing an oppositely directed current in the brain. The strength of the magnetic field decreases with distance; thus, only a few centimeters of the cortex are penetrated.

There is a vast variability of TMS protocols that are used to study different aspects of brain function:

(1) Single-pulse TMS: A single magnetic pulse is applied to the brain to study the excitability of the cortical neurons. This protocol is mainly used to study motor function and sensory processing.

(2) Repetitive TMS (rTMS): A series of magnetic pulses are applied in rapid succession to the brain. The frequency of the pulses can vary, leading to different neural effects. For instance, low-frequency rTMS (1-5 Hz) reduces the excitability of the neurons (Eldaief et al. 2011), while high-frequency rTMS (20-30 Hz) increases their excitability (Berlim and F Van den Eynde 2013; Chen et al. 2015). This protocol is mainly used to study transient neural plasticity.

(3) Theta-burst stimulation (TBS): this is a specific type of rTMS protocol that uses three pulses of magnetic stimulation at 50 Hz, applied at 5 Hz (Y. Huang et al. 2005). The effect of the stimulation can last up to 40 minutes while keeping the stimulation times short. Currently, this protocol is the one showing the longest-lasting effect (Fecteau and Eldaief 2014). Depending on the pattern of stimulation, the effect of TBS can be either facilitatory or inhibitory resulting in two different types of protocols:

►Continuous TBS (cTBS): In this method, TBS is applied continuously for a specific time, typically 40 seconds. cTBS is thought to have a prolonged inhibitory effect on the cortical neurons and is often used to reduce the excitability of a specific brain region.

►Intermittent TBS (iTBS): In this method, TBS is applied in bursts with a pause in between. Typically, each burst is delivered for 3 seconds with an inter-burst-interval of 15 seconds. iTBS is thought to have a prolonged facilitatory effect on the cortical neurons and is often used to increase the excitability of a specific brain region.

Stimulation can also be online (i.e., during the task) or offline (i.e., the task is performed soon after the stimulation is applied) (Fecteau and Eldaief 2014).

To investigate the relationship between brain activity and behavior a *"virtual lesion approach"* can be used. In this approach, TMS is delivered over a specific brain region, typically using cTBS which, as has been explained above, produces a temporary reduction in neural activity in the targeted area, mimicking the effects of a real lesion. This approach requires participants to perform a task while receiving (or soon after receiving) cTBS stimulation. This allows researchers to measure changes in performance and establish causal links between regions of interest (being modulated by the stimulation) and the resulting changes in behavior (e.g., changes in accuracy or reaction times).

In this context, picture naming tasks (i.e., the production of a noun or verb in response to a visually presented stimulus) have been widely used in combination with non-invasive brain stimulation (NIBS) protocols, including cTBS. In a recent meta-analysis (Klaus and Schutter 2018) the authors showed that this type of protocol can modulate performance during naming (e.g., by increasing naming latencies) with consistent alterations in reaction times, but little impact on accuracy. Overall, evidence indicates that areas showing a causal involvement during picture naming are the STG, the pMTG, the ATL, the AG, and the IFG (Acheson et al. 2011; Hoffman et al. 2012; Krieger-Redwood and Jefferies 2014; Mottaghy et al. 1999; Pobric, Jefferies, and Lambon Ralph 2010; Pobric, Jefferies, and Ralph 2007; Schuhmann et al. 2009, 2012; Shinshi et al. 2015; Töpper et al. 1998; Wagner and Rusconi 2023a).

When considering cTBS studies using language-switching paradigms during speech production evidence is scarce (summarized in Table 4).

Table 4. Summary of TMS studies using a language switching task in bilinguals. Detailed information about stimulation parameters, number of participants, target area, and observed effects is provided.

Study	N	Stimulation details	Target area	Effects
(Pestalozzi et al. 2020)	41	iTBS+ and cTBS- at 80% rMT	Left DLPFC	No behavioral effect
(Zhu and Sowman 2020)	16	cTBS- at 80% rMT	Right preSMA	Overall decrease in naming performance
(Nardone et al. 2011)	8	cTBS and iTBS at 80% rMT	Right DLPFC	No behavioral effect
			Left DLPFC	Increases and decreases in pathological switching
(Jost et al. 2020)	22	cTBS	Left DLPFC	No behavioral effect
(Ware, Lum, and Kirkovski 2021)	17	cTBS at 70% rMT	Left DLPFC	No behavioral effect

Most of these studies have targeted the left DLPFC based on previous neuroimaging evidence suggesting its importance in executive control, yet none of them found significant results at the behavioral level. Interestingly, two of these studies combined cTBS with EEG (Pestalozzi et al. 2020; Ware et al. 2021) and showed that, even though reaction times remained unaltered after stimulation, modulations at the neural level became evident. For instance, Ware et al. (2021) found that after cTBS over DLPFC, the N2 event-related potential (which is thought to index cognitive control), was reduced in switch trials compared to non-switch trials. Importantly, no change in the N2 was observed as a result of vertex or sham stimulation, supporting stimulation specificity.

Nardone et al. (2011) applied inhibitory and excitatory TBS to the left and right DLPFC on a bilingual patient who exhibited abnormal language switching following an ischemic stroke in the left frontal lobe. Interestingly, they found that excitatory stimulation of the left DLPFC temporarily interrupted abnormal language switching while inhibitory stimulation increased the number of utterances produced in the undesired language. There were no significant effects observed after stimulation of the right DLPFC.

Finally, one of these studies (Zhu and Sowman 2020) targeted the preSMA —another key region in the executive control network and observed a generally decreased performance in picture naming after cTBS. However, no specific modulations in the switch costs were found. This may also suggest that the preSMA plays a role in initiating speech in general but not in language switching *per se*.

Previous research using TMS to study language switching during speech production has primarily investigated two domain-general control regions: the left DLPFC and the preSMA. Although these regions have been associated with a range of executive demanding tasks, including language switching(Jiao et al. 2022), it remains unclear whether other brain regions identified in previous meta-analyses (e.g., (Luk et al. 2011)) and recent reviews (Tao et al., 2021) may play a distinct role in this process.

For instance, neuroimaging studies have shown that the angular gyrus (AG) and the posterior middle temporal gyrus (pMTG) are involved when bilinguals switch between languages (Abutalebi and Green 2016; Hernandez 2013), albeit exerting control at different levels (e.g., during the language task schema phase and the lexical selection phase, respectively). However, no study has yet examined their causal role in language switching. Thus, this thesis aims to address this gap by investigating the potential causal contributions of the AG and pMTG in bilingual language control. By doing so, we aim to identify brain regions beyond the classical domain-general control ones (e.g., DLPFC) that could be involved in the neural mechanisms supporting language switching in bilingual individuals.

1.5 Current work

1.5.1 Goals of the present thesis

Having reviewed relevant literature on language control in bilinguals and provided an overview of the current understanding of the topic, I will now proceed to explain the specific goals and methodology implemented in this thesis, and how it contributes to addressing existing gaps in the research field.

In summary, despite a significant amount of research on this topic, there is still no clear agreement on the specific mechanisms that underlie language control in bilinguals. In particular, there is a lack of understanding of the spectro-temporal patterns supporting this process and how these patterns may be affected by the presence of a brain tumor. Furthermore, neuroimaging evidence suggests that the AG and the pMTG are involved in the selection and inhibition of the appropriate language at different levels. However, their causal role in language control awaits experimental testing.

The goal of this thesis is two-fold: 1) To expand our knowledge of the neural mechanisms underlying bilingual language control in both neurotypical individuals and brain tumor patients through the use of multiple research methods such as behavioral, MEG, and TMS; 2) To apply this knowledge to improve preoperative and intraoperative mapping in brain tumor patients, minimizing the risk of long-term cognitive deficits following tumor resection.

To reach these goals, this work focuses on answering three main questions:

1) What are the spectro-temporal and spatial signatures of bilingual language control mechanisms in the neurotypical population? To date, few studies are addressing this aspect (and no study exploring this topic during speech production in highly proficient bilinguals). Additionally, answering this question will provide a normative baseline for better understanding potential oscillatory compensation in bilingual brain tumor patients. Finally, these findings will help us to decide whether our language-switching task should be implemented for mapping eloquent areas in bilingual patients (i.e., evaluation of its sensitivity in tackling language control).

2) What happens when the bilingual brain must negotiate language control in the presence of a tumor? By studying patients with LGGs before undergoing tumor resection, we will investigate neuroplasticity mechanisms put in place to preserve language control in the presence of a growing tumor and how this may differentially impact L1 and L2 processing.

3) Can the effects of a real lesion (i.e., tumor) be "simulated" in healthy bilinguals using a non-invasive approach such as a "virtual lesion" induced by cTBS? The AG and the pMTG have been identified by previous neuroimaging research as key areas for language control in bilinguals but their causal involvement has not been proven yet. Thus, by transiently disrupting activity in these areas and measuring consequent behavioral changes in switch cost responses we aim to establish their causal role in bilingual language control.

1.5.2 Overview of the experiments

To answer these questions, I conducted four experiments (summarized in Figure 8). Briefly, in all these experiments I used a language-switching paradigm (see below for a detailed description of task and stimuli) to investigate language control in highly proficient bilinguals. In Experiments I and II, the target population were healthy highly proficient Spanish-Basque speakers. Due to the COVID-19 pandemic, the pilot experiment for validating the task was conducted in online mode (Experiment I). Once restrictions were lessened, we were able to conduct Experiment II at the BCBL facilities and combine the same language-switching task with MEG recordings. Experiment III, on the other hand, was run in a group of highly proficient Spanish-Basque bilinguals harboring LGGs in their left hemisphere. In this case, all patients ran the same language-switching task in combination with MEG at the BCBL. Finally, to opt for the international Ph.D. title, I conducted a three-months internship at the Gervasutta Hospital in Udine (Italy). Experiment IV was conducted during my research stay abroad in a group of highly proficient Italian-Friulian bilinguals. This experiment combined the language switching task (plus a control task involving switching between semantic categories within each language) with a "virtual lesion approach" in which cTBS was applied over the AG, the pMTG, and an active control area (Vertex).

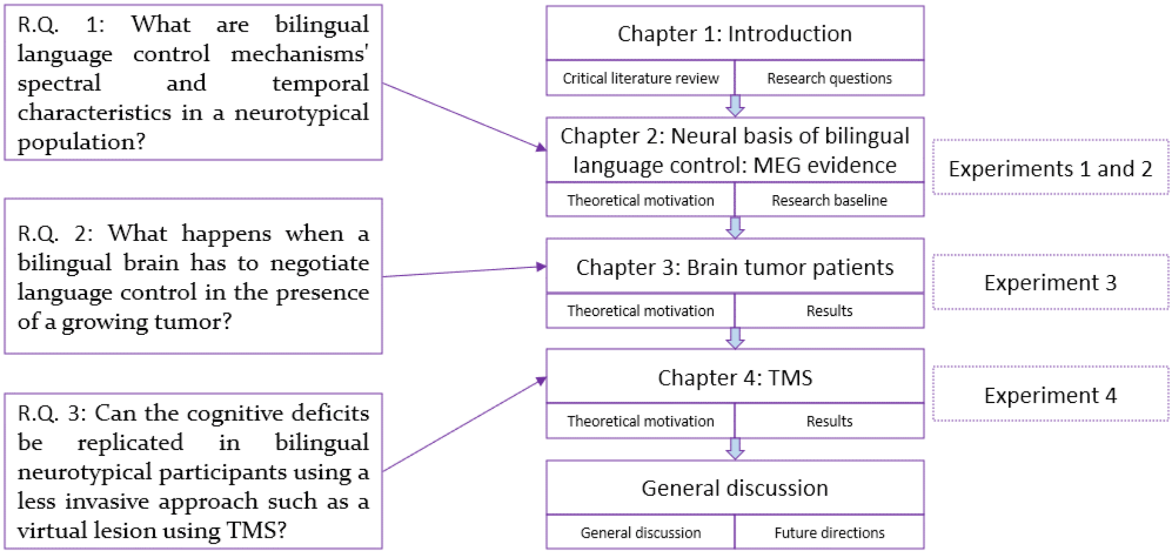


Figure 8. Overview of the experiments included in the present thesis

1.5.3 General Methodology

1.5.3.1 Stimuli and Task

Following previous switching paradigms (W. de Baene et al. 2015), we selected eight colorful hand-drawn pictures representing high-frequency objects as stimuli [Spanish/Basque names: "Perro"/"Txakurra" (dog); "Ventana"/"Leihoa" (window); "Oso"/"Hartza" (bear); "Gallina"/"Oiloa" (chicken); "Cuchillo"/"Labana" (knife); "Anillo"/"Eraztuna" (ring); "Camisa"/"Alkandora" (shirt); "Oreja"/"Belarria" (ear)]. The pictures were selected from a standardized battery developed by NEURE clinic® (https://www.neure.eu/) and matched in frequency. Frequencies for the Basque words were calculated using the E-hirz database(Perea et al., 2006)(Perea et al., 2006) and for Spanish, using EsPal (Duchon et al. 2013). The mean frequency for Basque words is 21.8 per million and 22.4 for Spanish.

Participants were asked to overtly name the pictures in either L1 or L2 depending on a color cue (e.g., red for L1 and green for L2) within the same block (i.e., mixed-language context) as fast and accurately as possible. The trial structure is depicted in Figure 9. A fixation cross appeared on the screen for 2 secs. Then the picture was presented for 2 secs, and participants overtly named the observed item (e.g., "Camisa"). Inter-stimuli interval (ISI) randomly varied between 0-1 secs. Reaction times and accuracy were collected online and stored for further preprocessing offline.

Overall, there were two types of trials: (a) those in which participants had to switch between languages from one trial to another (switch trials), and (b) those in which participants had to name a picture in the same language as in the preceding trial (non-switch trials). The proportion of switch to non-switch trials was 30/70%. To control for this proportion, the list of stimuli was pseudo-randomized. More specifically, a total of 336 pseudo-randomized trials were distributed into four conditions: (1) non-switch trials in L1 (118 trials), (2) non-switch trials in L2 (118 trials), (3) switch trials in L1 (50 trials), (4) switch trials in L2 (50 trials). Non-switch trials following a switch trial were eliminated to avoid the carry-over effects of switch trials; the first trial was also eliminated as it was impossible to quantify it as a switch or a non-switch trial. After the elimination, on average, 48 trials remained per condition.

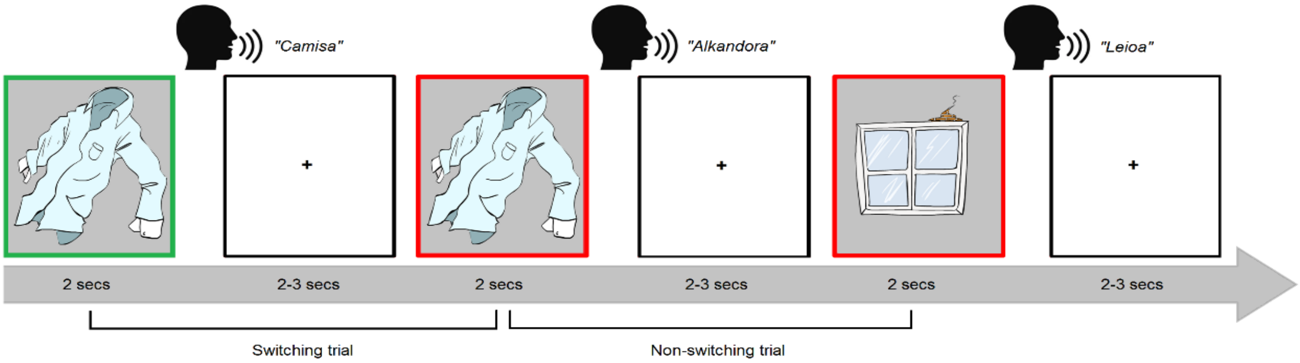


Figure 9. Examples of stimuli and experimental task.

1.5.3.4. Behavioral Assessment

Verbal responses were recorded using the participant's hardware of choice (e.g., headphones, microphone, built-in microphone). For safety reasons and to make online data collection possible, the audio files were recorded as .webm files encoded in a base64 string. For processing speech data, I developed a semi-automated open-source in-house software ("SPONGE") using Python (https://github.com/Polina418/Audio_processing). I used the software to decode and convert the audio files into .wav format, semi-automatically detect speech onsets (with online manual correction), and perform speech recognition using Google Cloud Speech-to-Text API. Speech recognition results were manually corrected offline. The software is described in more detail in the next section.

Reaction times were measured as the interval between the picture presentation and the onset of the participant's verbal response, disregarding all background noise preceding the target response. Trials in which the participant made a mistake or mumbled prior to the target word (e.g., "Hmmm, dog") were excluded from further analysis. Switch costs were calculated per participant by subtracting the mean response time on non-switch trials from the mean response time on switch trials. On average, 3% of responses were discarded.

1.5.3.5 “SPONGE”

At the moment of data collection and analysis of data for this thesis, there was no existing flexible, open-source code/software that would decrease the time needed to analyze audio responses from the participants. The idea of this software took inspiration from human speech processing and was written entirely in Python with the implementation of Google Cloud Speech to Text API to account for accuracy. The workflow of the software is presented in Figure 10.

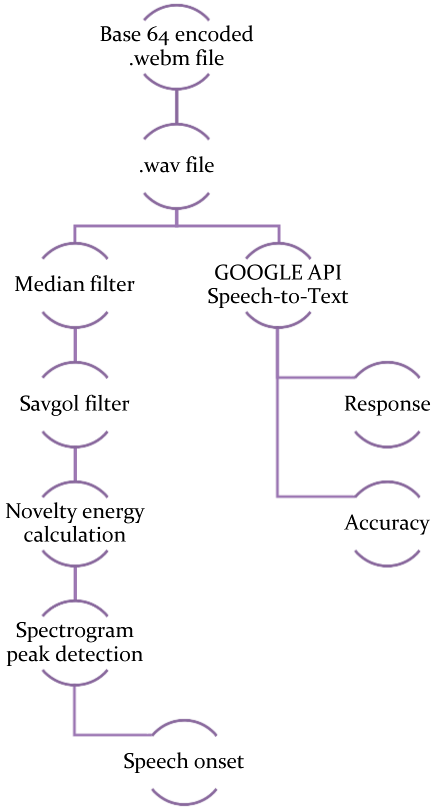


Figure 10. Workflow of the SPONGE software.

For this thesis, I needed both reaction times and accuracy of the vocal responses, so the software consists of 2 main parts: speech recognition and signal processing to get speech onsets. Speech recognition was implemented by connecting to cloud computing from Google, where there are trained models of many different languages recognizing speech with high accuracy.

First, a median filter was applied for the speech onsets, a non-linear digital filtering technique. This technique is frequently used for noise reduction on images or signals. The main idea is that this filter uses a moving window and replaces the central value of the window with a median of the surrounding elements. After that, a Savitzky-Golay filter was applied (Savgol), a digital filter that smooths the data without disturbing the signal tendencies using convolution.

When the signal is clearer, I identify the speech onset, which often comes with a sudden increase in the signal´s energy. To detect those changes, I used a novelty energy calculation function.

Different types of novelty energy can be calculated. For this software, I used an energy-based novelty function that consists of several steps:

1) Computing the local energy
2) Computing the first-order difference in the energy
3) Half-wave rectification of the first-order difference

Mathematically, this process can be described by the following formula:

Let x: Z→R be our signal of interest. Furthermore, let ω: [−M:M] →R for some M∈N be a bell-shaped window function centered at time zero (e.g., a Hann window). The local energy of x with regard to ω is defined to be the function E^{x}_{ω}:Z→R given by

$$E^{x}_{\omega} = \sum_{m \in Z} |x(m)\omega(\mathrm{m}-\mathrm{n})|^2$$

$$|r|_{\geq 0} := {r + |r|}/{2} = \begin{cases} r, & if\ r \geq 0 \\ 0, & if\ r < 0 \end{cases}$$

for r∈R. Altogether, we obtain an energy-based novelty function Δ_{Energy}: Z→R, given by

$$\Delta_{Energy}(n) := \ |E^{x}_{\omega}(n-1) - \ E^{x}_{\omega}(n)|_{\geq 0}$$

After this step, finding the onsets gets down to finding the peak of these differences.

After identifying the peaks, the software performs spectrogram analysis to find the most probable candidates for speech signals. A spectrogram of the filtered signal is calculated, and the first time slot is recorded. Then, these candidates are compared to the peaks found in the first part to exclude those most likely noise components.

1) Finding peaks in the spectrogram
2) Discard those peaks that are not speech-related

To control for errors, I added a manual correction. When the software detects a speech onset or multiple speech onsets, it asks if the onset detected is the correct one. Also, if detected, you can manually change it when the speech recognition is ambiguous (accuracy less than 70%). It will ask to clarify if that word is correct or to enter the word after playing it

This software works well on very noisy signals and signals with less noise. The proposed workflow works very well with fMRI or very noisy recordings, whereas there is an option to run a simplified procedure if the data at hand is less noisy.

The code is freely available at https://github.com/Polina418/Audio_processing

CHAPTER 2: Neural basis of bilingual language control in the healthy brain: MEG evidence

Motivation

The goal of this chapter is two-fold: 1) to fill the gap on the role of neural oscillations in bilingual language control during speech production and 2) to provide a baseline to further compare with LGG patients' data, assisting the interpretation of potential divergent patterns indicating language reshaping/compensation in patients.

Given these aims, we investigated the behavioral, spectro-temporal, and spatial correlates of bilingual language control in two independent groups of highly proficient Spanish-Basque bilinguals. Specifically, we ran two experiments. In Experiment I, participants completed the switching task online, requiring them to name pictures in a mixed-language context (i.e., alternating between naming in either Spanish or Basque within the same block depending on a color cue). Experiment II mimicked Experiment I, the only difference being that it was run at the BCBL facilities while MEG signals were simultaneously recorded.

First, based on previous evidence suggesting that highly proficient bilinguals show similar switch costs when switching from L2 to L1 and from L1 to L2, we expected a symmetrical behavioral effect. Second, based on previous literature on the oscillatory dynamics involved in bilingual language control, we anticipated differences between switch and non-switch conditions in low-frequency bands namely, in the theta (4-8 Hz) and the alpha (8-13 Hz) bands in a time window between ~200ms and ~500ms, where the lexico-semantic process takes place. Finally, given that linguistic and executive control processes are closely intertwined, at the neuroanatomical level, we expected the engagement of language-specific areas (e.g., left STG/MTG, ATL) but also fronto-parietal hubs involved in domain-general cognitive control.

2.1 Methods

2.1.1. Participants

Forty-six Spanish-Basque bilingual speakers were recruited through the BCBL Participa website (https://www.bcbl.eu/participa/) and received monetary compensation for their participation in the experiment. Twenty-five individuals performed the behavioral switching task online (M = 27.4 years; SD = 5.22, 9 females) (Experiment I). The remaining twenty-one performed the same task at the BCBL while MEG activity was continuously recorded (M = 25.04 years; SD = 3.94, 16 females) (Experiment II).

Before the experiments, all participants performed a language background questionnaire to collect detailed information about language use and proficiency levels. Language proficiency was measured employing the Basque, English, and Spanish Test [BEST] (de Bruin, Carreiras, and Duñabeitia 2017), using the semi-structured interview part of the test, which taps fluency, lexical resources, grammatical aspects, and pronunciation (Likert-like scale with scores ranging from 1 to 5). The cut-off criteria for considering an individual as a highly proficient bilingual were scores ≥ 4 in their L2. Furthermore, the composite scores were used for assessing the percentage of language exposure to Spanish and Basque. The scores were calculated by averaging self-reported listening, writing, and speaking percentages in each language. These scores were further normalized using the min-max method. This method is commonly used for data normalization, and it preserves the relationships among the original data values. Higher scores indicate higher exposure to a language and are calculated as shown in (1)

$$v_i' = \frac{v_i - min_A}{max_A - min_A}, \qquad (1)$$

where v' is a new, normalized value, v is the original value, min_A is the minimum value in the range, and max_A is the maximum.

All participants were right-handed, assessed via the Edinburgh Handedness Inventory (Oldfield, 1971), and had normal or corrected-to-normal vision. They all acquired their two languages in early childhood and had similar proficiency levels and exposure to both. Only five participants from the behavioral experiment reported Basque being their L1, and four from those who performed the MEG part. I will refer to Spanish as L1 and Basque as L2, as Spanish was the language most of the participants reported to be their L1. None of the participants reported significant medical, neurological, or psychiatric disorders. Before their inclusion in the study, all participants provided their written informed consent. The study protocol was approved by the Ethics Committee of the Basque Center for Cognition, Brain, and Language (BCBL) and was carried out following the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Four participants were removed from Experiment I due to the low quality of the audio recordings. In Experiment II, two participants were discarded from the final analysis due to a high number of blinking/muscular artifacts in the MEG recording (e.g., leading to > 40 trials in some conditions). Thus, final analyses were performed on a reduced sample of nineteen participants in Experiment I and twenty-one participants in Experiment II.

Table 5. Spanish-Basque participants' demographic data and linguistic profiles.

	Language	Mean	SD	*P*-value	W	Cohen's *d*
Spanish/Basque						
Experiment I: Behavioral Experiment Spanish/Basque						
Age (years)		27.4	5.22			
Gender		9f / 16m				
Interview (0-5)	Spanish	4.92	0.28	0.121	68.0	0.495
	Basque	4.76	0.44			
AoA (0-6 years)	Spanish	0.6	1.7	0.259	29.0	-0.363
	Basque	1.32	1.93			
Composite score (0-1)	Spanish	0.38	0.3	0.331	185.0	0.233
	Basque	0.3	0.24			
Experiment II: MEG Experiment						
Age (years)		25.04	3.94			
Gender		16f / 5m				
Interview (0-5)	Spanish	4.96	0.08	0.11	67.0	0.47
	Basque	4.83	0.29			
AoA (0-4 years)	Spanish	0.47	1.28	0.162	21.0	- 0.462
	Basque	1.28	1.7			
Composite score (0-1)	Spanish	0.5	0.29	0.10	163.0	0.41
	Basque	0.3	0.29			

2.1.2. Statistical analysis

Reaction times (RTs) obtained in the language switching task were log-transformed and analyzed using linear mixed models. Language, Condition, and their interaction were coded as fixed effects; while subjects and images were coded as random effects. The analyses were performed in R (R Core Team, version 4.1.3) using the lme4 package (version 1.1–29) (Bates et al. 2015) and lmerTest package (version 3.1-3) (Kuznetsova, Brockhoff, and Christensen 2017). P-values and degrees of freedom were obtained using Satterthwaite's method.

As is common practice, I attempted to fix the maximal number of random effects structure and reduce it to achieve convergence by eliminating correlations between random slopes or removing random slopes themselves. This process is called model simplification and it aims to reach convergence, meaning that the model finds a solution, providing reliable and interpretable estimates.

Models' assumptions (e.g. collinearity, normality of residuals, variance inflation factor) were verified using the performance package for R (Lüdecke et al. 2021).

2.1.3. MEG and MRI data acquisition

MEG data were acquired in a magnetically shielded room at a sampling rate of 1000 Hz using a 306-channel (102 magnetometers and 204 planar gradiometers) Elekta Neuromag system (Helsinki, Finland). MEG signals were recorded at a 1 kHz sampling rate and online filtered at a bandwidth of 0.1–330 Hz. The participant's head position inside the helmet was continuously monitored throughout the experiment using five head-position indicators (HPI) coils. Six electrode pairs were used to measure horizontal and vertical ocular and cardiac activity. The standard fiducial landmarks (i.e., left and right pre-auricular points and nasion) plus ~300 additional points registered over the scalp and eyes/nose contours were digitalized and used to spatially align the MEG sensor coordinates to the native T1 high-resolution 3D structural MRI of each participant. T1s were acquired with a Siemens 3T magnetom prismafit MR scanner (Siemens, Munich, Germany) in a separate session with the following parameters: echo time = 2.97ms, non-switching time = 2530ms, flip angle = 7° and field of view = 256 x 256 x 176 mm3, number of axial slices = 176, slice thickness = 1 mm, in-plane resolution = 1 mm × 1 mm.

2.1.4. MEG data preprocessing

Continuous data were preprocessed offline using the temporal extension of the signal space separation method (tSSS) (Taulu S and Simola J 2006) implemented in Maxfilter 2.2 (Elekta-Neuromag). Briefly, tSSS subtracts external magnetic noise from the MEG recordings, corrects for head movements, and interpolates bad channels. Subsequent analyses were performed using the MatlabR2014B and FieldTrip toolbox version 20170911 (Oostenveld R et al. 2011). Recordings were down-sampled to 500 Hz and segmented into epochs time-locked to picture presentation from 1000ms before image onset to 1000ms after image onset.

A semi-automatic procedure was employed to remove epochs containing electromyographic artifacts, SQUID jumps, and flat signals. Finally, a fast independent component analysis (fast ICA) was used to identify components reflecting blinks and electrocardiographic artifacts (Jung T P et al. 2000). Two participants were discarded from the final analysis due to a high number of blinking/muscular artifacts in the MEG recording. Thus, the final MEG analysis was performed on a reduced sample of nineteen participants.

2.1.5. MEG data analysis

Time-frequency representations (TFR) were calculated on clean MEG data epochs in the theta (4-7 Hz), and the alpha (8-13 Hz) frequency bands. These frequency bands were selected based on a recent review showing that switching effects in bilinguals mainly involve these brain rhythms (Tao et al. 2021). TFRs were obtained using a Hanning tapers approach and a fixed window length of 500ms, advancing in 10ms steps. Power was estimated separately for each orthogonal direction of a gradiometer pair and then combined, resulting in 102 measurement sensors. Power was calculated as the relative change with respect to a ~500ms pre-stimulus baseline. We used cluster-based permutation tests for the statistical contrasts at the sensor level (Maris and Oostenveld 2007). We averaged over frequency bins and time points in two specific time windows of interest to assess power differences: 100-350ms and 350-600ms after picture onset. These time windows were chosen based on data inspection and neurophysiological evidence, suggesting that recordings not contaminated with articulatory activity can be safely acquired around this time window in overt speech production tasks.

The permutation *p*-value was calculated using the Monte-Carlo method with 1,000 random permutations. The significance testing threshold was a *p*-value below 5% (two-tailed).

2.1.6. Source reconstruction

Source reconstruction was performed on the statistically significant effects observed at the sensor level. Individual T1-weighted MRI images were segmented for each participant into different brain tissues using the Freesurfer software. Co-registration between the MEG sensor space and the participant's MRI coordinates was done by manually aligning the digitized head surface and fiducial points to the outer scalp surface using MRIlab (Elekta Neuromag Oy, version 1.7.25). The forward model was calculated using the Boundary Element Method (BEM) implemented in the MNE suite (RRID: SCR_005972) (Gramfort et al. 2014) for three orthogonal tangential current dipoles, placed on a homogeneous 5-mm grid covering the whole brain. The forward model was reduced to the two principal components of the highest singular value for each source, corresponding to sources tangential to the skull. All sensors (i.e., planar gradiometers and magnetometers) were used for source estimation, normalizing the signal of each sensor by its noise variance (i.e., 500ms baseline period before picture onset). Brain source activity was calculated using a Linearly Constrained Minimum Variance (LCMV) beamformer approach (van Veen BD et al. 1997). The covariance matrix used to derive beamformer weights was estimated from the time-frequency window of the significant sensor-level effects and an equally sized baseline period before picture onset. To perform group-level analysis, brain maps were transformed from the individual MRIs to the standard Montreal Neurological Institute (MNI) by applying a non-linear transformation using the spatial-normalization algorithm implemented in SPM8.

Comparisons between conditions were performed with the location-comparison method (Bourguignon, Molinaro, and Wens 2018). This method generates bootstrap group-averaged maps to build a permutation distribution of location difference between local maxima in the two conditions being compared and test the null hypothesis that this distance is zero. Local maxima are defined as sets of contiguous voxels displaying higher power than all other neighboring voxels. The threshold for statistical testing at $p < 0.05$ was computed as the 95-percentile of the permutation distribution. All supra-threshold local MEG peaks were interpreted as indicative of brain regions likely triggering the sensor-level effects. The significant local power maxima coordinates were statistically compared across participants using t-tests.

2.2 Results

2.2.1 Behavioral results

Naming accuracy in all participants was at ceiling (Spanish: Mean = 99.4, SD = 1.1; Basque: Mean = 99.5, SD = 0.96); thus, statistical analyses were only performed on the RTs.

As fixed effects for the LMM, I entered Language, Trial type, and their interaction. Apart from the fixed effects, the model included Participants and Items as random effects (random intercepts). *P*-values were obtained using Satterthwaite's method. The analysis was performed in R (R Core Team, version 4.1.3) using the lme4 package (version 1.1–29) (Bates et al. 2015) and lmerTest package (version 3.1-3) (Kuznetsova et al. 2017).

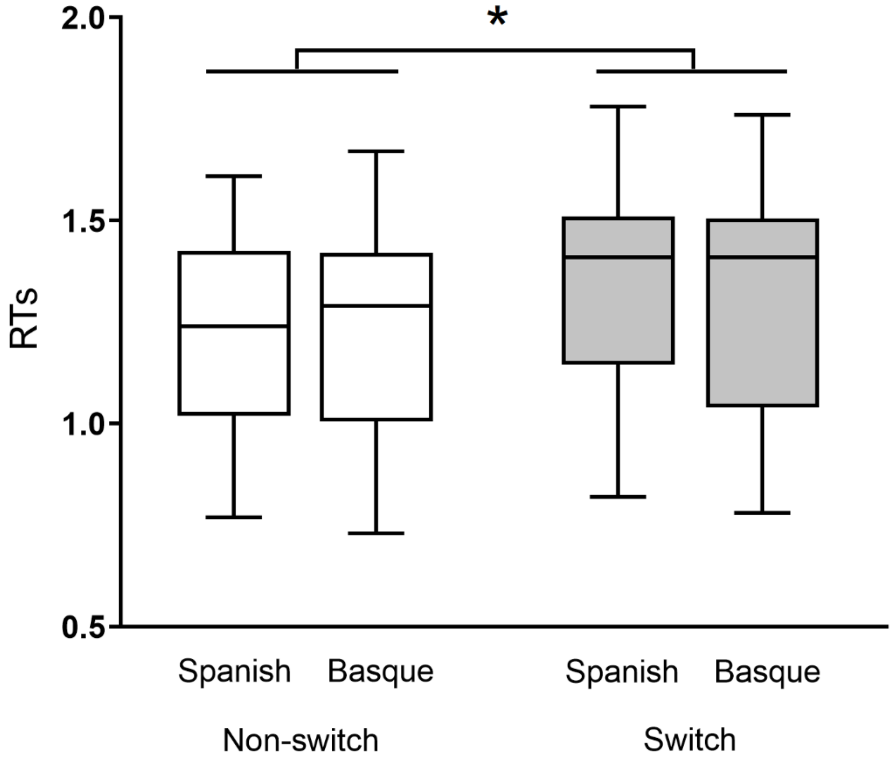


Figure 11. Behavioral performance during language switching. Mean reaction times (in seconds) for non-switch and switch trials in Spanish and Basque. Bars indicate SD. Asterisks indicate significant differences between conditions.

The final model had the following form:

$$\log(RT) \sim condition*language + (1|image) + (1|subject)$$

Table 6. Results of LMM for the Experiment I

	Effects of Language Switching					
Predictors	*Estimates*	*SE*	*CI*	*df*	*Statistic*	*p*
(Intercept)	0.23	0.04	0.14 – 0.31	4070.00	5.20	**<0.001**
Condition	0.04	0.00	0.03 – 0.04	4070.00	8.38	**<0.001**
Language	0.01	0.01	-0.00 – 0.03	4070.00	1.39	0.164
Condition*Language	0.01	0.00	-0.00 – 0.01	4070.00	1.40	0.162
Random Effects						
σ^2	0.07					
$\tau_{00\ \text{Image}}$	0.00					
$\tau_{00\ \text{ID}}$	0.04					
ICC	0.39					
N_{Image}	209					
N_{ID}	23					
Observations	4077					
Marginal R^2 / Conditional R^2	0.013 / 0.399					

Table 7 shows the results from the LMM for Experiment I. The effect of Trial type was significant (z = 8.38, p < 0.001), but the effect of Language and the interaction between Language and Trial type did not reach significance (z = 1.39, *p* = 0.164 and z = 1.4, *p* = 0.162, respectively). Switch trials (Mean = 1.33; SD = 0.251) were overtly named slower than non-switch trials (Mean = 1.24; SD = 0.24). Switch costs across Spanish (Mean = 0.106 secs) and Basque (Mean = 0.073 secs) were similar.

2.2.2 Sensor level results

First, a cluster-based permutation analysis was used to test for the effect of Language (Spanish vs. Basque) and Trial type (switch vs. non-switch). Then, following state-of-the-art pipelines for testing an interaction effect via a cluster-based permutation approach (www.fieldtriptoolbox.org/faq/how_can_i_test_an_interaction_effect_using_cluster-based_permutation_tests/); I subtracted switch and non-switch conditions within each language and compared the two differences. Overall, the effect of Language and the interaction did not reach significance (all ps > 0.05) in any of the frequency bands (i.e., theta and alpha) or time windows (i.e., early and late). However, there was a significant effect on the Trial type (Fig. 12A), as highlighted by a negative cluster in the alpha frequency band (8-13 Hz; Monte Carlo p = 0.01, two-tailed), showing stronger power decreases for the switch condition as compared to the non-switch one. This effect occurred in the late time window and was localized in the right combined gradiometers (Fig. 12B).

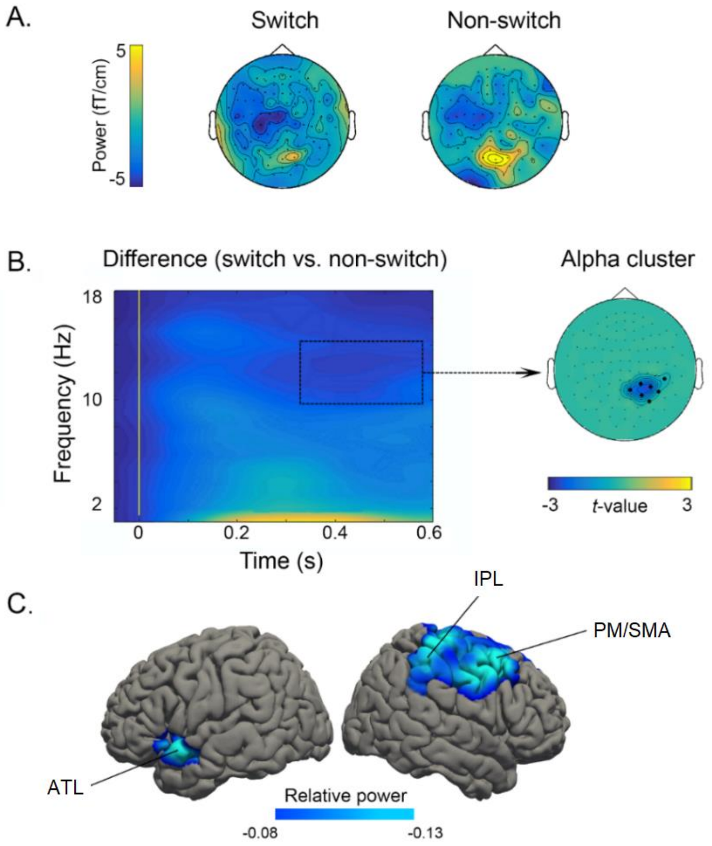


Figure 12. Sensor level results. (A) Topographic distribution plots for switch and non-switch conditions in the alpha frequency band (8-13 Hz) between 350-600ms after object picture onset. (B) Time-frequency representation (TFR) showing the difference between switch vs. non-switch conditions across languages in the combined gradiometers highlighted by the significant alpha negative cluster. (C) Localization of alpha peaks (switch vs. non-switch) circumscribed to the time interval highlighted by the significant cluster. All plotted regions reached a p-value < 0.01.

2.2.3 Source level results

Oscillatory effects at the sensor level were reconstructed at the source level on the frequency band and time window highlighted by the significant cluster. Alpha peaks identified for the switching effect (switch vs. non-switch trials across languages) were localized in the right inferior parietal lobe (BA39/40), the right premotor/supplementary motor area (BA6), and the left anterior temporal lobe (BA38, see Fig. 12C).

2.3 Summary and interim conclusions

This chapter investigated the behavioral, spectro-temporal, and spatial signatures supporting language control in highly proficient bilinguals by examining language switching in production.

1. Behavioral results revealed overall slower responses in switch as compared to non-switch trials. Notably, the difference between these two conditions (i.e., the switching cost) showed comparable magnitudes across Spanish and Basque replicating previous findings of symmetrical switch costs in bilinguals with similar L1-L2 proficiency.
2. MEG time-frequency results revealed comparable neural switch costs in Spanish and Basque, showing significant power decreases in the alpha band (8-13 Hz) for the switch as compared to the non-switch trials, irrespective of the language in use.
3. This effect was source-localized in domain-general (e.g., right IPL and PMA/SMA) and language-specific (left ATL) regions.

Overall, I provided behavioral and neuroimaging evidence for the existence of a common control mechanism in highly proficient bilinguals, which supports language selection and controlled access to lexico-semantic representations during speech production. More specifically, the switch and neural cost symmetries found in the present chapter suggest that bilinguals with similar proficiency in their L1 and L2 recruit a language-independent control mechanism during language production. These findings offer new insights into the role of parieto-prefrontal alpha oscillations in cue-based language selection and in mediating the controlled access to lexico-semantic representations in the ATL, likely inhibiting the non-target lexical form and/or disinhibiting the target one.

CHAPTER 3: Evidence from bilingual brain tumor patients

Motivation

The general aim of this chapter is to investigate how bilingual individuals cope with the presence of brain tumors affecting areas involved in language control.

Based on the critical literature previously reviewed and the normative data obtained from healthy highly proficient bilinguals in Experiments I and II, this chapter hypothesizes that bilingual patients with brain tumors will employ compensatory strategies to preserve their language control abilities. It is anticipated that this may involve the stronger engagement of executive control regions and the recruitment of a more widespread brain network, potentially including additional areas not typically present in neurotypical individuals.

3.1 Methods

3.1.1 Participants

A total of five Spanish-Basque bilingual patients with brain tumors in their left hemisphere. They all had normal hearing and normal or corrected to normal vision. Individual patients' demographics, lesions, and clinical characteristics are summarized in Table 7 (see Figure 12 for 3D reconstructions of the lesions). Patients were recruited at the Hospital Universitario Cruces Bilbao (Spain), where they received their diagnosis and underwent awake brain surgery for tumor resection (MD. Ph.D. Santiago Gil-Robles—Head of the Neurosurgery Department of the Hospital Universitario Quirón salud Madrid, Spain—, and M.D. Iñigo Pomposo Gastelu—Head of the Neurosurgery Department of the Hospital Universitario Cruces Bilbao, Spain—were neurosurgeons in charge). The initial neurological examinations at the hospital revealed no motor, somatosensory, or linguistic deficits. Patients were evaluated approximately one week before the surgery at the BCBL. Behavioral, MEG, and structural MRI data were collected in each session.

A battery of standardized neuropsychological and linguistic tests was used to evaluate participants' relevant linguistic and cognitive abilities. This battery included measures of general cognitive status as assessed via means of the 30-point screening Mini-Mental State Examination (MMSE) (Folstein, Folstein, and McHugh 1975); verbal and non-verbal intelligence measured using the

KBIT (Kaufman & Kaufman, 2014), and language production in Spanish and Basque via means of the BEST test (described in the general introduction).

A summary of the patient's demographic and clinical data can be found in Table 7.

Table 7. Clinical and demographic characteristics of the patients

ID	Age	Gender	Education	Handedness	Tumor location	Tumor volume (cm^3)
1	22	M	High school	R	Temporal	62.55
2	46	F	University	R	PreSMA	33.01
3	38	F	University	R	Temporo-insular	7.94
4	32	F	Postgraduate	R	PreSMA	13.2
5	31	F	Master	R	Prefrontal cortex	23.96

3.1.2. MRI data acquisition and lesion mapping

All participants underwent an MRI session separately in a 3T Siemens Magnetom Prisma Fit scanner (Siemens AG, Germany). High-resolution T1- and T2-weighted images were acquired with a 3D ultrafast gradient echo (MPRAGE) pulse sequence using a 64-channel head coil with the following acquisition parameters: FOV = 256; 160 contiguous axial slices; voxel resolution 1x1x1mm3; TR = 2530ms, TE = 2.36ms, flip angle = 7˚. For each patient, the origin of the T1/T2 weighted images (pre- and post-surgery) was set to the anterior commissure. Functional event-related scans consisting of 320 echo-planar images were acquired using a T2*-weighted gradient-echo pulse sequence with the following parameters: field of view: 192 mm; matrix = 64 x 64; echo time = 30ms; repetition time = 2 s; flip angle = 90 degrees. The volume comprised 33 axial slices with 3 mm isotropic voxels without slice gaps. The first six volumes of each functional run were discarded to ensure steady-state tissue magnetization.

Lesions were manually drawn using the MRIcron software (Rorden, Karnath, and Bonilha 2007) on the native space of participants' T1-weighted MPRAGE image by one of the neurosurgeons in charge of the patients' awake craniotomy. In addition, information from T2-weighted images was used when lesion boundaries were not clear in the T1. The lesion was then normalized to the MNI template, and one of the team members checked the alignment between the delignated lesion and the lesion in the native space. A volume of interest (VOI) was created for each patient. The extent of resection (EOR; in cm3) was measured on postoperative imaging as: (Volume of (preoperative

3D Tumor Reconstruction ∩ postoperative Resection) * 100/preoperative tumor volume). See Figure 13 for lesion delineation.

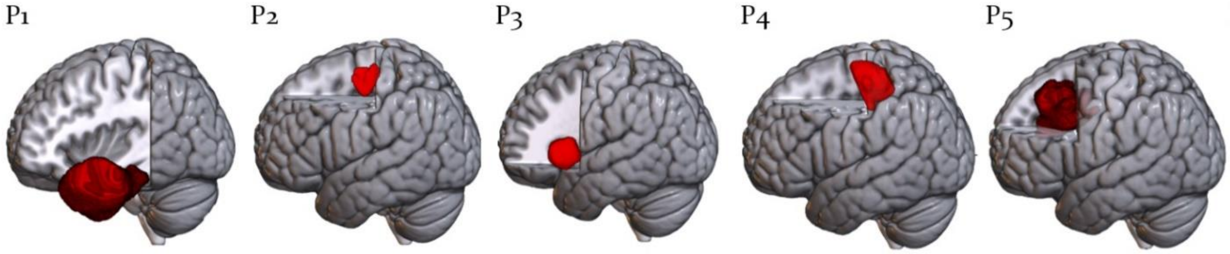


Figure 13. 3D reconstruction of tumor locations for each patient

3.1.3. Statistical analysis

The comparison between patients and the neurotypical population was performed using Crawford-Howell's (1998) *t*-test (Crawford and Garthwaite 2012; Crawford and Howell 1998) for case-control comparisons implemented in R. In this analysis, reaction times for each patient were compared to the corresponding reaction times from the neurotypical group of bilinguals.

3.2. Results

3.2.1. Cognitive and linguistic assessment results

Individual data points for each of the variables are shown in Figure 14. Overall, results show a typical neurological evaluation, with preserved language production abilities (as shown by performance in the BEST), normal IQ (as evinced by KBIT scores), and preserved cognitive status (as indicated by MMSE scores).

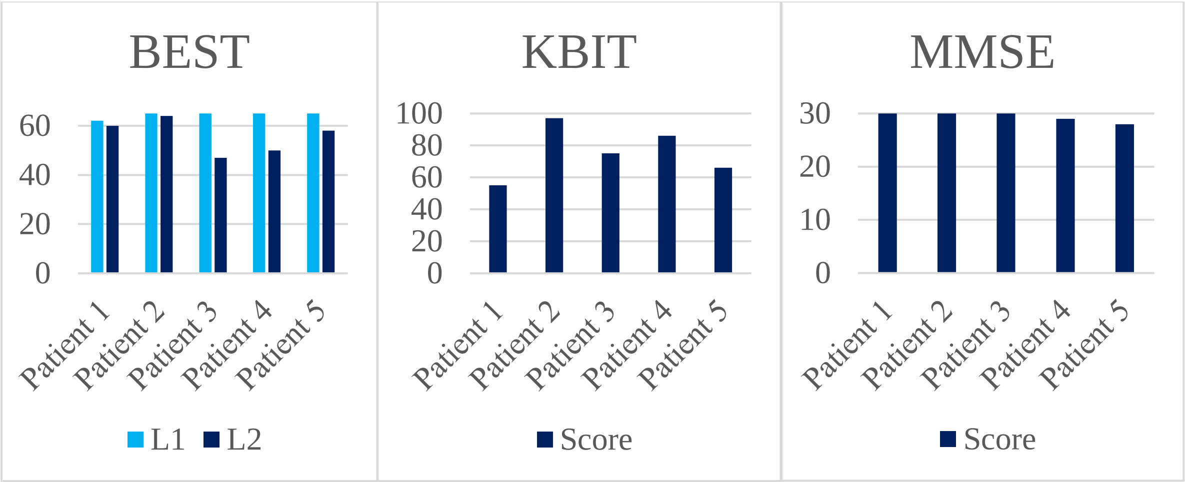


Figure 14. Language and cognitive evaluation in patients. Performance (%) in the BEST for L1 and L2 (Left panel), KBIT (Middle), and MMSE (Right) for all LGGs patients.

3.2.2 Behavioral results

Naming accuracy in all patients was at ceiling (Spanish: Mean = 99.6, SD = 0.31; Basque: Mean = 99.7, SD = 0.47); thus, statistical analyses were only performed on the RTs.

Crawford's *t*-tests comparing RTs from each patient with those of the neurotypical group showed no significant differences in switch and non-switch trials across languages (Spanish Mean = 1.18 sec, SD = 0.04, Basque Mean = 1.13 sec, SD = 0.15) (all *p*s > 0.05). Furthermore, no differences were observed in Spanish and Basque "switch costs" between patients (Spanish Mean = 0.12, SD = 0.04, Basque Mean = 0.09, SD = 0.04) and neurotypicals (Spanish Mean = 0.11, SD = 0.01, Basque Mean = 0.07, SD = 0.02), overall suggesting preserved language control abilities in patients.

3.2.3 Sensor level MEG results

Here, I replicated the preprocessing pipeline and statistical analysis used in Experiment II (see 2.1.4, and 2.1.5 subsections). Overall, there was a significant effect on the Trial type (Fig. 15 1A), as highlighted by a negative cluster in the alpha frequency band in the late time window (8-13 Hz; Monte Carlo $p = 0.01$, two-tailed), showing stronger power decreases for the switch condition as compared to the non-switch one. This effect occurred in the late time window and was localized in the right occipito-parietal combined gradiometers. The effect of Language (Fig. 15 2A) also reached significance in the alpha band but in the early time window (8-13 Hz; Monte Carlo *p* = 0.01, two-tailed), showing stronger power decreases for Spanish as compared to Basque. The effect was localized in right fronto-temporal combined gradiometers. The interaction did not reach significance (all *p*s > 0.05) in any of the frequency bands (i.e., theta, alpha) or time windows (i.e., early and late).

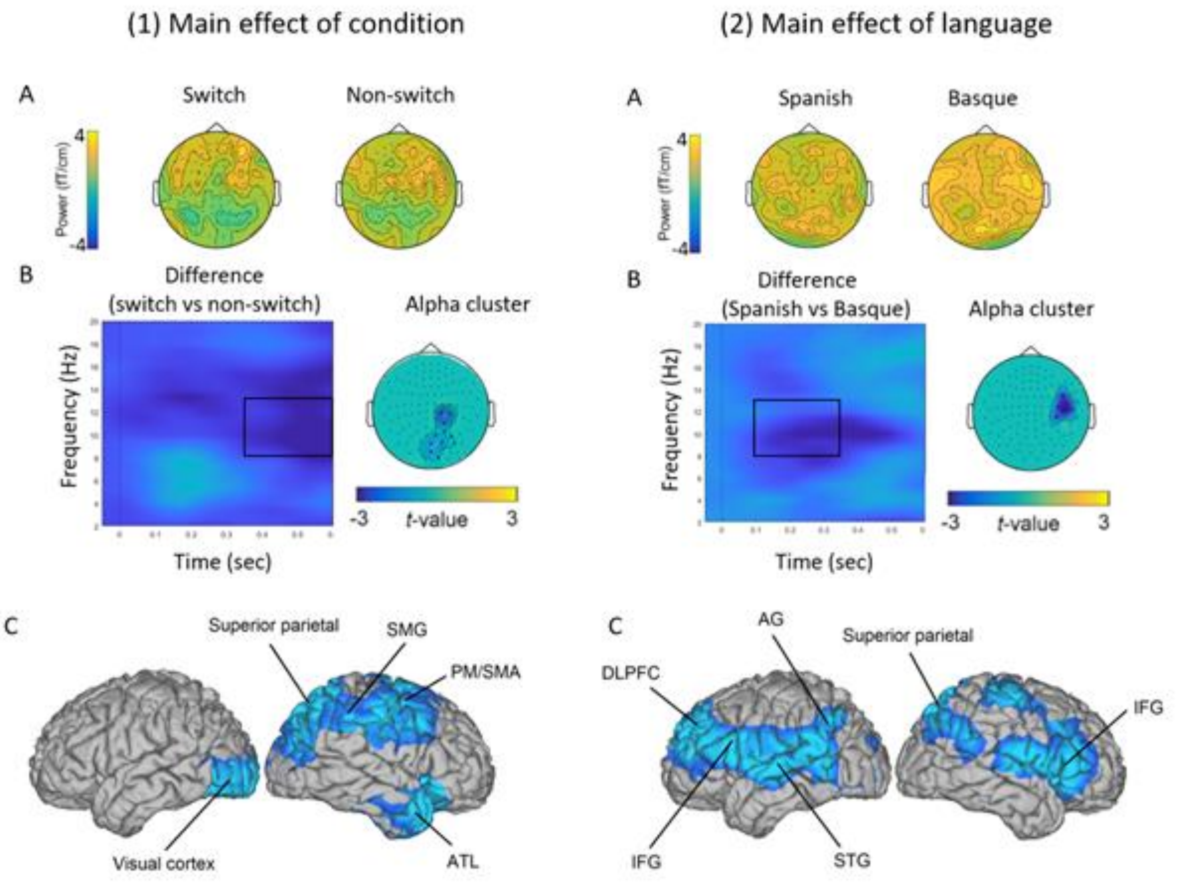


Figure 15. Sensor level results. (1) Main effect of Condition, (2) Main effect of Language. (A) Topographic distribution plots for the switch and non-switch trials in the alpha frequency band (8-13 Hz) between 350-600ms after object picture onset. (B) Time-frequency representation (TFR) showing the difference between switch vs. non-switch trials in the combined gradiometers as highlighted by the significant negative alpha cluster. (C) Localization of alpha peaks (switch vs. non-switch) circumscribed to the time interval highlighted by the significant cluster. All plotted regions reached a *p*-value < 0.01.

3.2.4 Source level results

At the source level, patients exhibited a highly right-lateralized network for the main effect of the Condition including the involvement of superior and inferior parietal regions (SMG, AG), PM/SMA, and ATL, while also engaging the left visual cortex, which was well expected given the visual nature of our task (i.e., involving object pictures). Source localization of the language effect engaged a widespread network, including bilateral IFG, left DLPFC, left STG, left AG, and right superior parietal regions.

3.2.5. Comparison between MEG patterns in LGGs patients and healthy bilinguals

At the sensor level, both healthy bilinguals and patients showed a similar main effect of Condition in the late time-window, involving stronger alpha (8-13 Hz) power decreases for the switch as compared to non-switch trials. At the source level, similar areas were also recruited including regions in the right IPC and the right PM/SMA. However, while healthy bilinguals showed activation in the left ATL, patients showed maximal peak activity in the right contralateral homolog. This might be explained by the fact that one of the patients (patient 1) had the left ATL completely infiltrated by the tumor, leading to the recruitment of the contralateral healthy homolog to overtake the function supported by the damaged area.

On the other hand, only patients showed the main effect of Language at the sensor level, with stronger alpha (8-13 Hz) power decreases for Spanish as compared to Basque in an early time-window. Source localization of this effect recruited domain-general (e.g., dlPFC, superior parietal) as well as language-specific regions (e.g., STG) together with a bilateral engagement of IFG, possibly reflecting increased cognitive demands during lexical selection processes (Thompson-Schill, D’Esposito, and Kan 1999). While, at the behavioral level, switch costs were comparable between patients and healthy bilinguals irrespectively of the language in use, qualitatively, reaction times for Spanish were overall slower as compared to Basque. Together with the MEG evidence (i.e., stronger alpha desynchronization for Spanish vs. Basque), this possibly suggests that the processing of the L1 became more effortful in the presence of the tumor. Previous evidence from bilingual patients with LGGs suggests indeed that this could be the case (Gatignol, Duffau, et al. 2009). The authors provide different explanations for this phenomenon. First, it could be that the order of language recovery follows the order of language acquisition. If L1 was acquired first in life, then it is expected to be recovered later.

3.3 Summary and interim conclusions

Taken together, several insights can be drawn from this experiment.

1. At the behavioral level, patients with brain tumors elicited similar switch costs as those observed in healthy bilinguals, while it must be noted that processing of L1 (and not L2) becomes overall slower across patients.
2. At the oscillatory level, a similar effect of Condition was found across groups. In addition, patients showed an early effect of Language in the alpha band in the right sensors with stronger power decreases for L1 as compared to L2. These results align with the behavioral observations, suggesting that a higher effort is needed to produce utterances in L1 vs. L2 in the presence of a brain tumor.
3. At the source level, domain-general and language-specific regions were recruited during language switching. Interestingly, beyond the areas recruited by neurotypicals, patients showed the engagement of a wider network additionally comprising contralesional healthy homologs in the right hemisphere.

Overall, in the present chapter, I provided behavioral and neuroimaging evidence for the existence of functional compensation during language switching in bilingual patients with brain tumors. Indeed, at the behavioral level, patients and controls showed comparable reaction times, which speaks in favor of successful compensation leading to function preservation. At the oscillatory level, patients showed a similar parieto-prefrontal alpha pattern - as the one found in healthy bilinguals - for switch vs. non-switch trials (i.e., similar topography and timing), further supporting the preservation of a common inhibitory mechanism involved in the controlled access to lexico-semantic representations during speech production. However, patients evinced a Language effect that was absent in controls. The timing of this effect, occurring in an early time window, and the involvement of domain-general control regions suggests that inhibitory control targeted another stage of processing, likely reflecting inhibition at the “task schema” level, possibly reflecting difficulties in maintaining task goals signaled by the cue (i.e., which language to use).

CHAPTER 4: TMS

Motivation

Neuroimaging research has shown that both the left AG and the pMTG are active during language tasks involving semantic control under conflicting situations (Noonan et al. 2013). However, when it comes to language control —and potential conflict arising from interference between languages in bilinguals, only the left AG seems to play a critical role (Abutalebi and Green 2016).

Neuroimaging techniques, however, are blind to causal relationships between brain areas and cognitive functions. In this context, repetitive TMS protocols such as cTBS provide a non-invasive approach that can fill this gap.

This chapter aims to determine the causal involvement of the left AG in bilingual language control. This will be of great help to predict neural and behavioral patterns following awake craniotomies in bilingual patients. Indeed, using DES in a healthy population is not possible due to its invasiveness, and TMS constitutes a viable method to test the role of specific brain areas in cognition, by modulating neural activity and measuring consequent behavioral effects.

Specifically, I hypothesized that the left AG would be involved in controlling language interference during switching, whereas the left MTG would not. To test this hypothesis, I used a cTBS protocol to target these areas, while highly proficient Italian-Friulian bilinguals performed a language-switching task. As a control task, I used two monolingual switching tasks with the same design as the bilingual switching task, but instead of switching between languages, the participants were asked to switch between semantic categories (objects and verbs). This control task allowed us to test the specificity of AG stimulation in the bilingual switching task. This experiment was performed at the Gervasutta hospital in Udine (Italy), where I performed a three-moths internship to opt for the international Ph.D. title.

4.1 Methods

4.1.1. Participants

For Experiment IV, sixteen Italian-Friulian bilingual speakers (M = 23.07 years, SD = 2.18, 12 females) were recruited at the Gervasutta Hospital in Udine in Italy, and performed the switching tasks at the hospital after cTBS. In this particular case, beyond the language switching task used in previous studies, we additionally implemented a control task to better isolate the contribution of the AG and the pMTG in switching performance. Briefly, the control task consisted of two blocks in which participants had to switch between naming the object (e.g., “shirt”) or an associated action (e.g., “dress”) separately for each language. Thus, this design allowed us to better measure specific switching performance between languages while controlling for semantic control during category switching. Importantly, pictures, color cues, and overall structure of the task (e.g., the proportion of switch and non-switch trials) remained the same as in the original language-switching task.

All participants were right-handed, did not report any neurological disorders, and met the safety requirements for performing a TMS experiment. They were not taking any psychiatric medication and had no history of fainting, headaches, epilepsy, or seizures. Every participant signed an informed consent form after the instructions. The experimental procedures were approved by the local ethics committee (*Comitato Etico Regionale Unico*, Friuli Venezia Giulia, Italy) and were carried out in accordance with the revised Helsinki Declaration (World Medical Association General Assembly 2008).

All participants acquired their two languages (Italian and Friulian) in early childhood and had similar exposure to both. Further on, I will refer to Italian as L1 and Friulian as L2, as Italian was the language most participants reported as their L1.

All participants taking part in Experiments IV completed a questionnaire to evaluate language history and daily use patterns in Italian/Friulian. This questionnaire was adapted from (Gatignol, Hugues, et al. 2009) (see Appendix 4). For all participants, the composite score was individually calculated taking into account self-evaluation scores for speaking, comprehension, and reading. Composite scores were calculated following the same procedure as described for Spanish/Basque bilinguals. The frequency of use was also calculated as a composite score of the languages reported to be used daily in different environments (home, work, university, and friends). The score represents the percentage of daily use of the two languages.

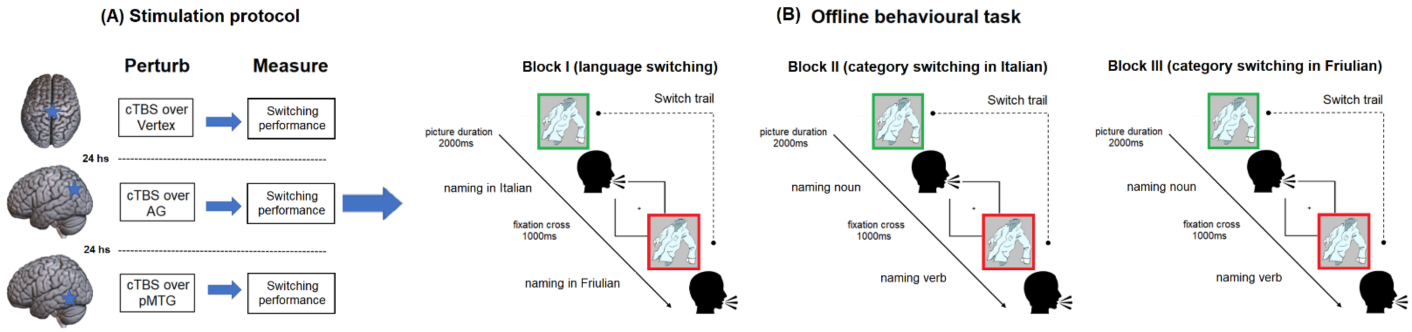
Three participants were discarded from the experiment given that they did not complete the three stimulation sessions (see below). Thus, final analyses were performed on a reduced sample of fourteen participants.

Table 8. Italian-Friulian participants' demographic data and linguistic profiles.

	Language	Mean	SD	*P*-value	W	RBC
Experiment IV: TMS Experiment						
Age (years)		23.07	2.18			
Gender		11f/5m				
AoA (0-6)	Italian	1.04	1.6	0.764	26.5	0.076
	Friulian	0.84	1.656			
Composite score (0-1)	Italian	0.94	0.126	1.0	45.0	-0.011
	Friulian	0.65	0.328			
Frequency of use (0-1)	Italian	0.63	0.3	0.198	40.5	0.473
	Friulian	0.367	0.3			

4.1.2. Experimental design and procedure

Figure 16. Experimental design



Participants were tested individually at the Gervasutta Hospital in Udine, Italy. Before the beginning of the experiment, the examiner explained the set-up, the TMS functionality, risks, and possible side effects to the participant, and the participant signed the consent forms. The participants were also informed that they could withdraw from the participation at any point if they became uncomfortable.

Each participant was tested in 3 separate sessions (see Figure 16). Each session was separated by at least 24 hours. The testing order for the target (AG and pMTG) and control area (vertex) was counterbalanced across participants. After each stimulation session, each participant performed the 3 different blocks offline: the language switching block, a category switching block in Italian, and a category switching block in Friulian). The order of the blocks was counterbalanced across participants.

4.1.3. Neuronavigation

The coil position for cTBS stimulation was identified on each participant's scalp with the SofTaxic Navigator system (EMS, Italy). Skull landmarks (nasion, inion, and preauricular points) and 65 points providing a uniform representation of the scalp were digitized using a Polaris Vicra Optical Tracking System (NDI, Canada). Coordinates were automatically estimated by the SofTaxic Navigator from an MRI-constructed stereotaxic template. The precise locations (i.e., coordinates) were identified from previous studies discussed in Chapter 1. For AG, the coordinates stimulated were (x= -48, y= -62, z = 37), and for the MTG, (x = -58, y = -50, z = -10). The vertex, which served as an active control site, was defined as the intersection of the midpoints between the nasion and inion and right and left fiducial points. This location was determined with tape measurement, and the desired coil position was marked for later use. The average coordinates for the vertex across participants were (x =-1, y = -8, z = 79). All coordinates are in MNI space. See Figure 17.

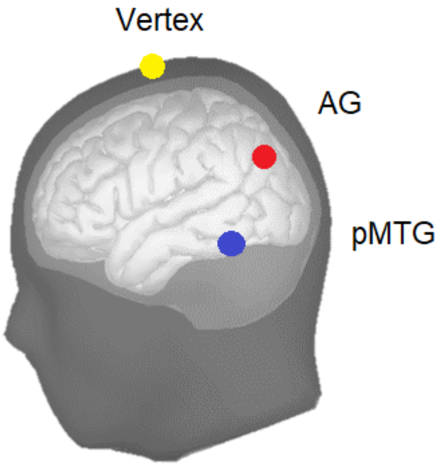


Figure 17. Vertex, AG, and pMTG coordinates stimulated during the TMS experiment

The participant wore a hat with reflective spherical markers steadily fixed on it, which were tracked by the navigation system in real-time. No adverse effects during cTBS were reported or noticed in any participant.

4.1.4. cTBS

The cTBS protocol consisted of three pulses delivered at 50 Hz, and the bursts were repeated at 5 Hz. As such, a total of 600 pulses were delivered over a period of 50 secs. Stimulation was administered with a 70mm Double Air Film Coil connected to a Magstim Rapid2 stimulator (The Magstim Company, Carmarthenshire, Wales, UK).

Following previous cTBS literature targeting language-related areas described in Chapter 1, stimulation intensity for each individual was calculated as 80% of their resting motor threshold (rMT). The rMT for each participant was identified before the experimental session and defined as the minimum intensity applied on the left primary motor cortex (M1) to elicit three visible twitches on the contralateral first dorsal interosseous (FDI) muscle out of five consecutive stimuli. Participants were instructed to keep their right hand's middle and big fingers touching in an “OK” sign but not contracted while the RMT was determined. Table 8 in Appendix D represents the participant's summary of motor coordinates, vertex coordinates, and average motor threshold. The average threshold across participants was 39.9% (range: 33% to 48%).

cTBS (Huang et al. 2005) was used offline to achieve transient disruption of the left AG and left pMTG baseline activity (as well as on Vertex as an active control site). After the “perturb session” with cTBS, it took no more than 5 minutes to start the “measure session”, which allowed us to capture the effect of the stimulation when it reached its maximum (Huang et al. 2005). This repetitive TMS protocol can induce a reduction of cortical excitability thought to be mediated by long-term depression-like mechanisms (Huang et al. 2007).

4.1.5. Data analysis

4.1.5.1 Language switching task

Independently of the stimulation area, naming accuracy was at ceiling (AG: Mean = 99.72%, SD = 0.11; MTG: Mean = 99.76%, SD = 0.22; Vertex: Mean = 99.8%, SD = 0.17); thus, statistical analyses were performed only on the RTs.

Individual RTs from the cTBS experiment (Experiment IV) were analyzed using linear mixed models (LMMs), with Language (Italian, Friulian), Trial type (switch, non-switch), and Site (Vertex, AG, MTG) as main effects. The model included by-subject, by-order (i.e., order of stimulation and block), and by-image (i.e., picture to be named) random intercepts. The final model specification for the analysis of the individual RTs obtained in the cTBS experiment was as follows:

log(RT) ~ condition*language*(AG-Vertex + pMTG-Vertex)+(1|order)+(1|subject)+(1|image)

Planned comparisons were used to make specific contrasts between the different levels of the categorical variable "Area" while controlling for the other variables in the model. In particular, I used orthogonal contrasts to account for the effect of the stimulation site on the outcome. I was interested in testing whether cTBS over AG and pMTG differed from cTBS over Vertex (active control region). To do so, I specified the following matrix of contrasts: $\begin{array}{ccc} Vertex & -1 & -1 \\ AG & 1 & 0 \\ MTG & 0 & 1 \end{array}$. By using orthogonal contrasts, we can reduce the number of comparisons being made and more accurately determine the effects of each area while maintaining statistical control over the Type I error rate inflation. Additionally, planned comparisons can be more powerful than post-hoc tests, since they are specifically tailored to the research questions at hand, making LMMs results more interpretable (Schad et al. 2020).

4.1.4.2 Category switching task

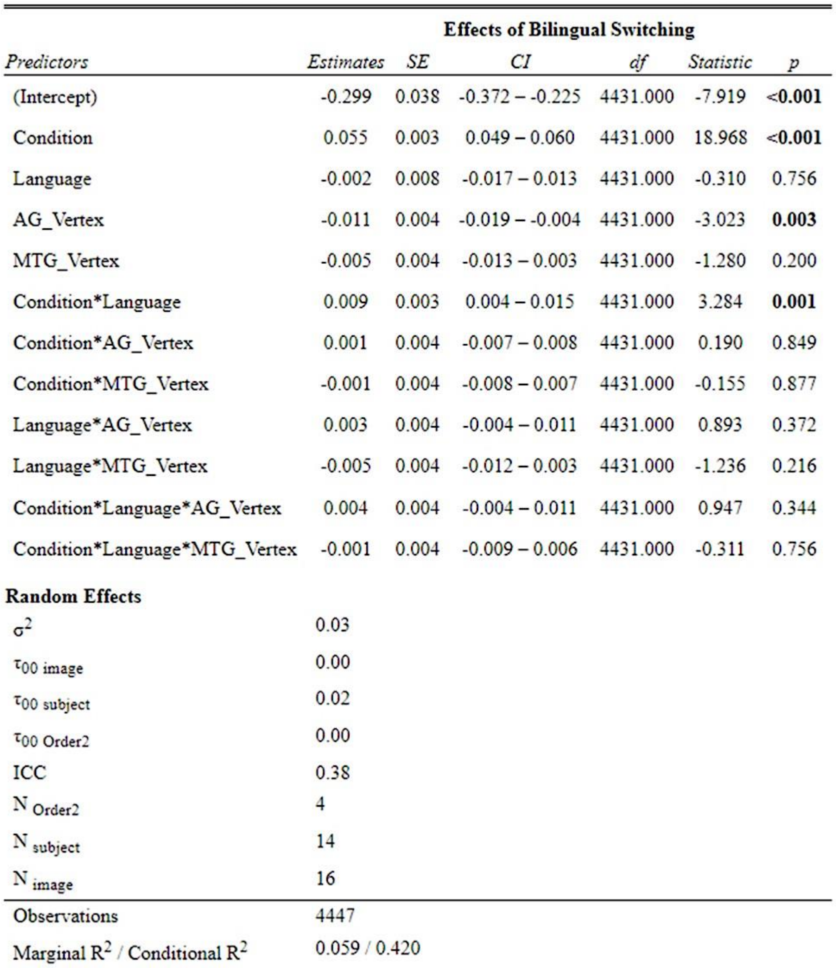
Independently of the stimulation area, naming accuracy was at ceiling (AG: Mean = 99.7%, SD =0.1; pMTG: Mean = 99.75%, SD = 0.1; Vertex: Mean = 99.7%, SD = 0.11) for Italian and (AG: Mean = 99.78%, SD = 0.07; pMTG: Mean = 99.67%, SD = 0.36; Vertex: Mean = 99.69%, SD = 0.29) for Friulian; thus, statistical analyses were performed only on the RTs. Individual RTs from the category switching blocks were analyzed using LMMs, with Language (Italian, Friulian), Trial type (switch, non-switch), Category (object, action), and Site (AG vs Vertex and pMTG vs Vertex) as main effects. As in the previous case, the model included by-subject and by-image random intercepts also including the order of the task in by-order intercept. The final model specification for the analysis was as follows:

log(RT) ~ condition*category*language*(AG-Vertex+pMTG-Vertex)+
(1|order) + (1|subject) + (1|image)

4.2 Results

4.2.1. Language switching task

Table 9. LMM results



	Effects of Bilingual Switching					
Predictors	*Estimates*	*SE*	*CI*	*df*	*Statistic*	*p*
(Intercept)	-0.299	0.038	-0.372 – -0.225	4431.000	-7.919	**<0.001**
Condition	0.055	0.003	0.049 – 0.060	4431.000	18.968	**<0.001**
Language	-0.002	0.008	-0.017 – 0.013	4431.000	-0.310	0.756
AG_Vertex	-0.011	0.004	-0.019 – -0.004	4431.000	-3.023	**0.003**
MTG_Vertex	-0.005	0.004	-0.013 – 0.003	4431.000	-1.280	0.200
Condition*Language	0.009	0.003	0.004 – 0.015	4431.000	3.284	**0.001**
Condition*AG_Vertex	0.001	0.004	-0.007 – 0.008	4431.000	0.190	0.849
Condition*MTG_Vertex	-0.001	0.004	-0.008 – 0.007	4431.000	-0.155	0.877
Language*AG_Vertex	0.003	0.004	-0.004 – 0.011	4431.000	0.893	0.372
Language*MTG_Vertex	-0.005	0.004	-0.012 – 0.003	4431.000	-1.236	0.216
Condition*Language*AG_Vertex	0.004	0.004	-0.004 – 0.011	4431.000	0.947	0.344
Condition*Language*MTG_Vertex	-0.001	0.004	-0.009 – 0.006	4431.000	-0.311	0.756
Random Effects						
σ^2	0.03					
$\tau_{00\ image}$	0.00					
$\tau_{00\ subject}$	0.02					
$\tau_{00\ Order2}$	0.00					
ICC	0.38					
N_{Order2}	4					
$N_{subject}$	14					
N_{image}	16					
Observations	4447					
Marginal R^2 / Conditional R^2	0.059 / 0.420					

The LMM analysis performed on the RTs showed a significant main effect of Condition (z = 18.9, $p < 0.001$) overall indicating that switch trials (Mean = 0.81, SD = 0.2) were overtly named slower than non-switch trials (Mean = 0.71, SD = 0.17).

The planned contrast between AG vs. Vertex (active control site), was significant (z = -3.02, p = 0.003), showing that after AG cTBS stimulation naming latencies across languages and conditions significantly increased (Mean = 0.78, SD = 0.21) as compared to the Vertex session (Mean = 0.77, SD =0.19). See Figure 18A. Notably, the contrast between pMTG and Vertex did not yield significance (p = 0.2).

Additionally, a significant Condition by Language interaction (z = 3.28, *p* = 0.001), indicated that in both languages, switch trials (Italian: Mean = 0.83, SD =0.11; Friulian: Mean = 0.81, SD =0.12) were overtly named slower than non-switch trials (Italian: Mean = 0.72, SD =0.10; Friulian: Mean = 0.73, SD =0.09; all *ps* < 0.001). In addition, switch trials were overtly named slower in Italian than in Friulian (*p* = 0.001), while non-switch trials did not differ across languages (*p* = 0.3). See Figure 18B.

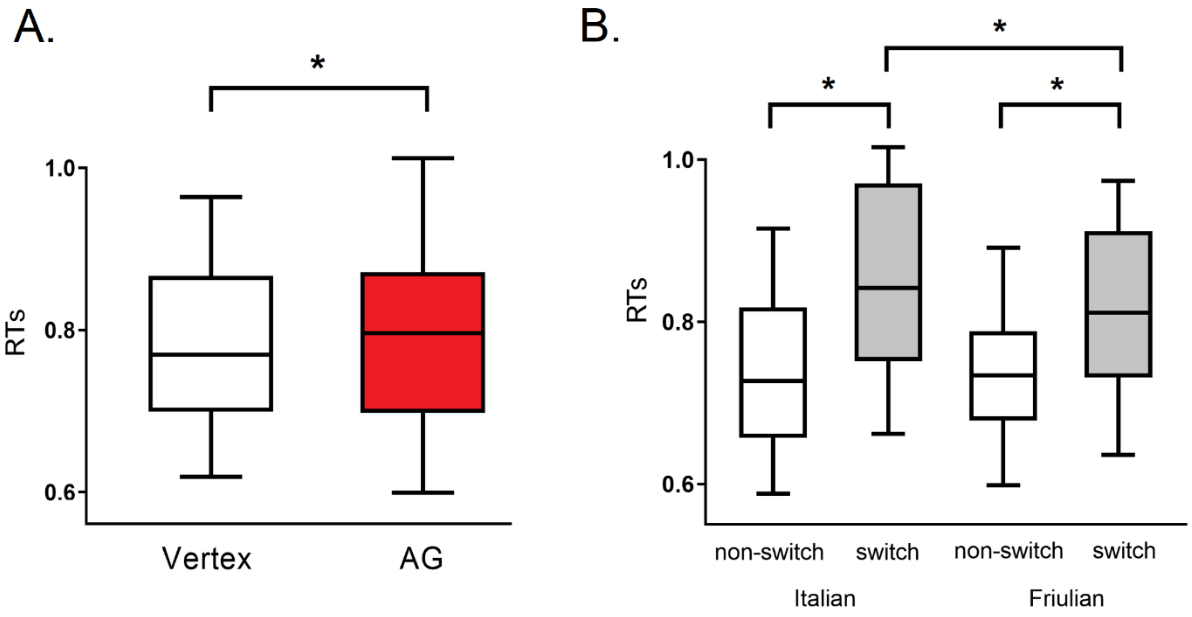


Figure 18. Language switching performance. (A) cTBS stimulation effect, with AG showing increased RTs as compared to Vertex (across conditions and languages). (B) Language (Italian, Friulian) by Condition (non-switch vs. switch) interaction across stimulation sites.

4.2.2 Category switching task

Table 10. LMM results for the category switching task

	Effects of Monolingual Switching					
Predictors	*Estimates*	*SE*	*CI*	*df*	*Statistic*	*p*
(Intercept)	-0.212	0.046	-0.303 – -0.121	9270.000	-4.558	**<0.001**
Condition	0.047	0.002	0.043 – 0.052	9270.000	19.662	**<0.001**
Category	0.073	0.010	0.054 – 0.092	9270.000	7.524	**<0.001**
Language	-0.053	0.002	-0.058 – -0.048	9270.000	-22.025	**<0.001**
AG-Vertex	-0.004	0.002	-0.007 – -0.001	9270.000	-2.313	**0.021**
MTG-Vertex	-0.011	0.003	-0.017 – -0.006	9270.000	-3.941	**<0.001**
Condition*Category	-0.015	0.002	-0.020 – -0.011	9270.000	-6.441	**<0.001**
Condition*Language	0.001	0.002	-0.004 – 0.005	9270.000	0.289	0.773
Category*Language	-0.003	0.002	-0.008 – 0.002	9270.000	-1.179	0.238
Condition*AG-Vertex	0.002	0.002	-0.001 – 0.006	9270.000	1.312	0.189
Condition*MTG-Vertex	-0.007	0.003	-0.012 – -0.001	9270.000	-2.433	**0.015**
Category*AG_Vertex	0.002	0.002	-0.001 – 0.006	9270.000	1.414	0.157
Category*MTG-Vertex	0.000	0.003	-0.005 – 0.006	9270.000	0.074	0.941
Language*AG-Vertex	0.005	0.002	0.002 – 0.008	9270.000	2.983	**0.003**
Language*MTG-Vertex	0.005	0.003	-0.000 – 0.011	9270.000	1.887	0.059
Condition*Category*Language	-0.001	0.002	-0.006 – 0.004	9270.000	-0.387	0.699
Condition*Category*AG-Vertex	-0.002	0.002	-0.005 – 0.001	9270.000	-1.256	0.209
Condition*Category*MTG-Vertex	0.007	0.003	0.002 – 0.013	9270.000	2.636	**0.008**
Condition*Language*AG-Vertex	-0.000	0.002	-0.004 – 0.003	9270.000	-0.269	0.788
Condition*Language*MTG-Vertex	-0.001	0.003	-0.007 – 0.004	9270.000	-0.443	0.658
Category*Language*AG-Vertex	0.001	0.002	-0.003 – 0.004	9270.000	0.370	0.711
Category*Language*MTG-Vertex	0.001	0.003	-0.004 – 0.007	9270.000	0.477	0.634
Condition*Category*Language*AG-Vertex	-0.003	0.002	-0.007 – 0.000	9270.000	-1.942	0.052
Condition*Category*Language*MTG-Vertex	0.000	0.003	-0.005 – 0.006	9270.000	0.058	0.954
Random Effects						
σ^2	0.05					
$\tau_{00\ \text{image}}$	0.00					
$\tau_{00\ \text{subject}}$	0.02					
$\tau_{00\ \text{Order2}}$	0.00					
ICC	0.33					
N_{Order2}	4					
N_{image}	16					
N_{subject}	14					
Observations	9298					
Marginal R^2 / Conditional R^2	0.124 / 0.416					

When considering the Category switching blocks, the LMM analysis performed on the RTs showed significant main effects of Condition (z = 19.66, $p < 0.001$), Category (z = 7.52, $p < 0.001$), and Language (z = -22.02, $p < 0.001$). Overall, as in the language switching block, switch trials (Mean = 0.88, SD =0.27) were overtly named slower than non-switch trials (Mean = 0.80, SD =0.25). In addition, when naming in Friulian (Mean = 0.89, SD =0.27) participants were overall slower than when naming in Italian (Mean = 0.8, SD =0.25). Finally, actions (Mean = 0.9, SD =0.27) were overtly named slower than objects (Mean = 0.78, SD =0.24).

A significant difference between AG and Vertex stimulation was observed (z = -2.3, $p = 0.02$), showing that after AG stimulation, naming latencies showed an overall decrease (Mean = 0.84, SD = 0.27) as compared to Vertex (Mean = 0.85, SD =0.26). This effect was overall stronger for Italian compared to Friulian as indicated by the interaction between Language and AG vs. Vertex (z = 2.98, $p = 0.003$).

When comparing pMTG with Vertex (z = -3.9, $p < 0.001$), a significant difference also emerged showing that after cTBS over the pMTG participants were overall faster in naming pictures (Mean = 0.83, SD =0.25) as compared to the Vertex session (Mean = 0.85, SD =0.26). 2). Importantly, this effect was further qualified by a triple interaction between Condition, Category, and pMTG vs. Vertex stimulation (z = 2.63, $p = 0.008$). See Figure 19.

This interaction indicated that switch trials (Vertex: object = 0.853; action = 0.942; pMTG: object = 0.80; action = 0.923) were named slower as compared to non-switch trials (Vertex: object = 0.725; action = 0.89; pMTG: object = 0.73; action = 0.863), with this effect being significant for objects and actions in both stimulation sessions (all *p*s < 0.001).

Crucially, after pMTG stimulation, participants became selectively faster in naming objects during switch trials ($p = 0.01$), whereas actions remained unaffected ($p = 0.83$).

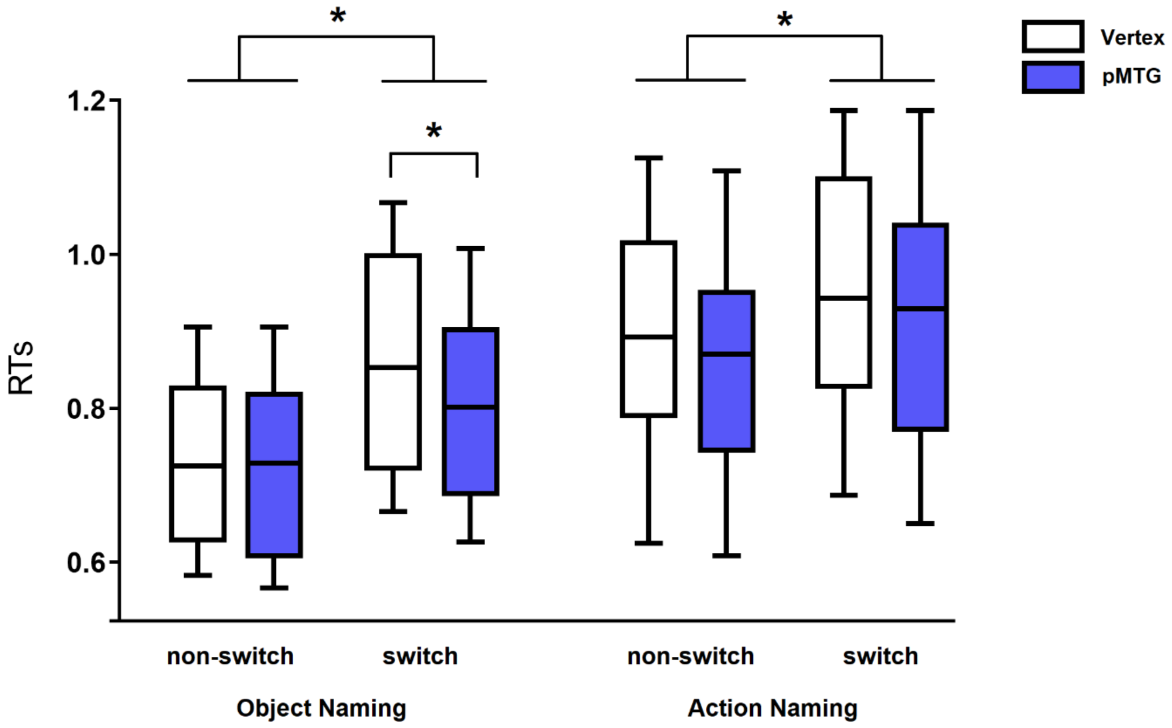


Figure 19. Triple interaction between Condition, Category, and MTG stimulation compared to Vertex during category switching blocks

4.3 Summary and interim conclusions

This chapter aimed to determine whether two critical areas - the left AG and left pMTG - previously reported to be involved in controlled language processing in bilinguals are causally engaged in language switching during speech production. The findings from this chapter can be summarized as follows:

1. cTBS over the AG led to significantly (i) increased RTs during the language switching block and (ii) decreased RTs during category switching blocks, as compared to Vertex stimulation.
2. cTBS over the pMTG did not produce any effect during the language switching block, but significantly decreased RTs during category switching blocks compared to Vertex stimulation. Moreover, this effect was specific to object naming during switch trials.

Overall, these results do not completely support the idea that the AG and pMTG play a causal role specifically during language switching in bilinguals. Instead, AG stimulation resulted in behavioral differences in both language and category switching blocks compared to Vertex stimulation, suggesting that this area has a broader domain-general role in picture naming during high cognitive situations. Additionally, the absence of any behavioral effects during the language switching block for pMTG stimulation indicates that this area does not play a causal role in switching between languages. However, our findings do support the notion that the pMTG is causally involved in the controlled lexico-semantic retrieval under executive demanding situations, and suggest that it plays a specific role in accessing object knowledge during speech production, as indicated by the decreased RTs for object naming during switch trials compared to Vertex stimulation.

CHAPTER 5: GENERAL DISCUSSION

5.1. Behavioral results

When considering behavioral findings, all bilingual speakers exhibited language switch costs (i.e., increased reaction times for switch vs. non-switch trials). This effect is well predicted by previous literature (Declerck & Philipp, 2015b), suggesting that switching involves an effort associated with system reconfiguration (i.e., choosing a different language from the one previously used). According to the IC model, one of the key mechanisms that underpin language switching is inhibition: bilingual speakers suppress the non-target language to properly produce a response in the target one (Abutalebi and Green 2007; Green 1998; Green and Abutalebi 2013). According to this view, if L1 and L2 proficiency levels are balanced, symmetric switch costs should be observed, indicating that the amount of inhibition deployed to control language interference is similar. The findings of symmetric switch costs align well with previous behavioral evidence (W. de Baene et al. 2015; Costa and Santesteban 2004; Costa et al. 2006; Köpke et al. 2021; Magezi et al. 2012), possible suggesting the existence of comparable levels of inhibitory control when bilinguals master their L2 in a native-like fashion.

Earlier research has indicated that differences in AoA affect language processing in bilinguals in addition to language proficiency. In our studies, all individuals acquired their L2 early in life. Furthermore, it has been suggested that the age of L2 acquisition has no significant role in the semantic domain (Indefrey 2006; Perani and Abutalebi 2005), the linguistic level mainly captured by our study. Thus, the effects observed in the present study seem to be primarily driven by participants' high proficiency levels rather than by the AoA.

These results were consistently observed across all experiments (including those involving neurotypicals and patients) and in both language groups (Spanish/Basque and Italian/Friulian), indicating that the task is reliable and the effects are robust, regardless of the language pair spoken by the highly proficient bilinguals.

Critically, patients did not show any significant differences compared to neurotypicals in reaction times, suggesting the existence of successful function preservation evidenced in similar responses at least at the behavioral level. Yet, it is important to mention that a qualitative evaluation of the reaction times showed that verbal responses for the L1 were overall slower than in the L2. These findings potentially highlight the increased demands for L1 processing in the presence of a tumor. L1 processing might be affected slightly more due to language recovery order, as was proposed by (Gatignol, Duffau, et al. 2009), where the order of recovery is reversed compared to the order of language acquisition.

5.2. MEG results

Behavioral results were mimicked at the oscillatory level. In other words, the lack of switch costs in behavior was reflected in a lack of neural costs -no effect of language or interaction between language and condition at the oscillatory level. Alpha power (8-13 Hz) was found to be significantly lower during the switch compared to non-switch trials for both languages, between 350 and 600 ms after picture onset. From a broader standpoint, alpha oscillations have been proposed as a hallmark of inhibitory control and, in particular, as a fingerprint of controlled access to semantic knowledge stored in long-term memory (Klimesch 2012; Klimesch, Freunberger, and Sauseng 2010; Sauseng et al. 2007). In the language domain, alpha power decreases in the aforementioned time window have been consistently linked to the lexico-semantic processing of object-related knowledge during speech production in monolingual (Piai and Zheng 2019; Quiñones et al. 2021) and bilingual individuals (Geng et al. 2022; Quiñones et al. 2021). In the context of language switching, while there is evidence for the role of alpha rhythms in language control during comprehension (Litcofsky and van Hell 2017), to the best of our knowledge, this is the first study reporting its involvement during overt speech production.

Source localization of the alpha switch vs. non-switch effect highlighted the involvement of language-specific (i.e., left ATL) and domain-general cognitive control regions (i.e., right parietal and PM/SMA). In highly proficient bilinguals, a similar activation pattern showing greater activity in the right IPL and PMC/SMA regions has been recently reported in neuroimaging studies for the switch as compared to non-switch trials (W. de Baene et al. 2015; Garbin G et al. 2011; Köpke et al. 2021). It has been proposed that bilateral parietal cortices mediate language selection (Abutalebi and Green 2008). In particular, during switching, the right IPL's role would be biasing selection towards the target language – while its left counterpart would be responsible for biasing selection away from the language no longer in use. Interestingly, a recent study (Sdoia, Zivi, and Ferlazzo 2020) applying anodal transcranial direct current stimulation (tDCS) over the right parietal cortex shows a selective performance improvement when switching to a recently inhibited task, supporting a broader role of this region in overcoming previous inhibition.

Similarly, the SMA has been implicated in proactive switching (Hikosaka and Isoda 2010) using contextual cues hinting at the need for a change toward a new behavior. For instance, disruptive repetitive TMS over the SMA selectively hampers individuals' performance during the cue period hinting at a switch trial (Rushworth et al. 2002), suggesting that this region mediates cue-based prospective reconfiguration. This proposal aligns well with the switching paradigm used in the present study, in which a color cue indicated to bilinguals whether a language change was required or not. Thus, the finding of parieto-prefrontal alpha oscillations mediating switching effects may reflect language selection based on cue processing.

On the other hand, the left ATL is known to house language-invariant semantic representations in bilinguals (Correia et al. 2014; Geng et al. 2022; Phillips and Pylkkänen 2021) and, in particular, object-related ones (Baldo et al. 2013; Buchweitz et al. 2012; Lambon Ralph, Pobric, and Jefferies 2009). Indeed, it has been recently shown that highly proficient bilinguals recruit ATL during object naming (Geng et al. 2022). Interestingly, the left ATL shows robust simultaneous activation with the other areas highlighted by our source analysis (i.e., PMC/SMA cortices) during task and rest (Jackson et al. 2016) and with the right inferior parietal cortex during language switching in highly proficient bilinguals (Zheng et al. 2020). Taken together, the source level results of the alpha effect suggest that the right parieto-prefrontal network is involved in biasing language selection towards the target language based on cue information (Abutalebi and Green 2008), enabling the controlled access to the appropriate lexico-semantic representation in the ATL, possibly via disinhibiting the target item and/or inhibiting the non-target one. Interestingly, alpha power decreases were comparable for both languages, supporting the idea that when bilinguals are balanced in their L1 and L2, the amount of inhibitory control is symmetrical not only at the behavioral level but also at the neural level.

In line with effects observed in neurotypicals, brain tumor patients showed a main effect of Condition, with stronger alpha power decreases for the switch as compared to non-switch trials. This effect occurred also in the same time window (~350-600ms) in which the lexico-semantic process takes place and involved similar brain regions as those engaged by neurotypicals. This suggests that brain tumor patients are able to preserve their language control abilities despite the presence of a tumor. However, patients showed an additional main effect of Language in the alpha band that was absent in neurotypicals. This effect occurred in an earlier time window (~100-350ms), indicating that it reflects a different stage of processing likely involving cue-based language selection

and reflected stronger inhibition for the L1 as compared to the L2. This effect was indeed source localized in a wide network of brain regions involving domain-general (e.g., DLPFC) and language-specific areas (e.g., STG).

A further point that requires discussion is that neuroimaging studies in highly proficient bilinguals have underscored the involvement of subcortical regions during language switching (Garbin G et al. 2011). Here, we used MEG brain recordings, which are more suited to capture cortical activity. Furthermore, the methodological approach used to source localize the sensor-level results is also biased toward detecting cortical effects. Thus, it cannot be entirely ruled out that some subcortical regions may have also contributed to the observed modulations, although this approach was not sensitive enough to detect them.

Finally, it is worth mentioning that contrary to our expectations, no differences were observed in the theta frequency band (4-7 Hz). Theta power increases have been widely implicated in switch cost effects across language switching (Fernandez, Litcofsky, and van Hell 2019; Litcofsky and van Hell 2017; Liu et al. 2015) and non-linguistic switching paradigms (Cooper et al. 2017; McKewen et al. 2021; Sauseng et al. 2006, 2007). For instance, studies reporting theta modulations during language switching (Litcofsky and van Hell 2017) and, in particular, during speech production (Liu et al. 2015) found power increases for switches into the L2 as compared to L1, suggesting a role for theta in controlling cross-language interference at the lexico-semantic level (i.e., inhibition of the dominant L1 and/or boosting of L2 representations). Nevertheless, these studies were performed on low-proficient bilinguals, an aspect that may explain the lack of theta effects in our study. Indeed, in a recent study from our lab (Geng et al. 2022), highly proficient bilinguals showed similar theta power increases in Spanish and Basque during overt picture naming. In our switching paradigm, the absence of this effect might reflect that when the L2 is mastered in a native-like fashion, activation levels across languages can be flexibly adjusted (e.g., by raising the activation of L2 representations). Alternatively, it has been suggested that as proficiency increases, competition and conflict resolution mechanisms require less control and become more automatized (Abutalebi 2008; Garbin G et al. 2011)

5.3. cTBS results

Neuroimaging studies have shown that, when bilinguals need to control for language selection in switching tasks, the left AG and the pMTG get involved. Here, we conducted a cTBS experiment targeting these two regions and tested their causal involvement in language switching. Overall, our findings provide weak evidence for a specific causal link between the AG and pMTG and language switching in bilinguals.

Our results suggest that the AG has a domain-general control role during highly demanding production tasks, as evidenced by the changes in behavioral responses observed during both language and category switching blocks. In other words, the causal involvement of the AG was not limited to language switching but also extended to switching between semantic categories. This aligns well with a recent review of studies measuring behavioral outcomes after (or during) TMS over the left AG (Wagner and Rusconi 2023). The reviewed evidence suggests a causal involvement of the left AG in a wide range of high-level cognitive tasks in which there is a strong contextual/semantic conflict, with this conflict being not restricted to the language domain.

Nevertheless, in our study, the AG showed distinct effects on language and category switching blocks, with an increase in RTs in the former and a decrease in the latter, compared to Vertex stimulation. Additionally, in the category switching block, the effect of AG stimulation interacted with Language, mainly affecting the Italian L1, pointing to a potential relationship between the AG and more language-specific processes.

Recent research suggests that the AG plays a role in exerting control during the "language task schema" phase, which refers to the mental representation or framework used by bilinguals to achieve a linguistic goal, such as producing speech in a specific language (Thomas and Allport 2000). These schemas regulate the output of the lexico-semantic system by biasing selection towards target representations while inhibiting non-target ones. Specifically, the AG seems to be critical for the selection and maintenance of task schemas (Green and Abutalebi 2013) based on contextual cues (Li et al. 2014). Indeed, previous evidence (Branzi et al. 2021) has shown that the AG is causally involved in language tasks that require the integration of contextual cues, as in the present study where color cues indicated the language in which participants had to name the pictures. Thus, the behavioral effects observed after disrupting AG activity may reflect interference with the processing of contextual cues and/or with the maintenance and selection of task schemas.

It is worth noting that the left AG was not activated in the MEG study conducted on healthy highly proficient bilinguals —which instead showed activation in the right AG. A recent meta-analysis (Sulpizio et al. 2020) shows that while proficient bilinguals typically show activation of the right AG during language switching, low proficient ones show instead activation in the left homologue. Thus, the absence of left AG involvement in healthy bilinguals might be well explained by their proficiency level. However, even though also being highly proficient, LGGs patients recruited the left AG. This suggests that the presence of a tumor can trigger the recruitment of additional control regions that may perform "background checks" when language demands are low (e.g., as in the case of healthy highly proficient bilinguals). TMS findings support this interpretation, by showing that the left AG seems to be engaged under highly demanding conflicting situations.

On the other hand, the stimulation over the pMTG led to faster reaction times as compared to Vertex only in the category switching blocks, showing no involvement during language switching. The pMTG is thought to be involved in the controlled access to lexico-semantic representations (Gold and Buckner 2002; Vandenberghe et al. 1996). It has been proposed that, in bilinguals, its involvement might be primarily related to managing competition between target and non-target lexical representations either within a language or between translation equivalents across languages. Our findings only support the former claim, as no language effect nor language interaction was observed with pMTG stimulation.

Overall, the finding of faster RTs after pMTG stimulation is supported by the "addition-by-subtraction" mechanism, which proposes that repetitive TMS can enhance cognitive function by disrupting processes that interfere, compete, or distract from task performance (Zhao et al. 2018). A similar effect has been observed in a recent study by Zhao et al. (2018), which found that cTBS over the pMTG (as compared to Vertex stimulation) led to faster reaction times in a task requiring the semantic integration of co-speech gestures in terms of their congruency (Zhao et al. 2018). Importantly, this study used a task that tapped into semantic processing, an aspect that aligns well with the experimental nature of the category switching task. Therefore, our finding of a specific reduction in RTs after cTBS over pMTG may indicate that the competing/distracting influence of the non-target semantic category was reduced, with this effect being irrespective of the language in use.

Last but not least, this reduction of RTs after pMTG stimulation was specific for switch trials involving object naming. This result is consistent with previous research indicating that the ventral pathway, of which the pMTG is a critical region, primarily underlies the semantic representation and retrieval of object knowledge (Amoruso et al. 2021; Gleichgerrcht et al. 2016; Shapiro, Moo, and Caramazza 2006; Vigliocco et al. 2011). Interestingly, in a recent study (Amoruso et al. 2021), we found that while patients with LGGs in ventral regions (including the pMTG), showed longitudinal (post- vs. pre-surgery) compensatory patterns for object naming, patients with LGGs in the dorsal fronto-parietal pathway showed instead a selective compensation for action naming.

5.4 Limitations and avenues for future research

The studies conducted in the context of the present thesis are not without limitations. First, the sample size of bilingual brain tumor patients is relatively small (n = 5), therefore these findings should be interpreted with caution. It is important to note, however, that recruiting this specific population (i.e., highly proficient bilinguals with low-grade gliomas) is a challenging task, and appropriate analytical methods (e.g., Crawford *t*-tests) were applied to analyze the data at the individual patient's level, thus ensuring the high scientific quality of the results. Nevertheless, future studies with larger sample sizes are needed to strengthen our conclusions. Second, our studies only focused on bilinguals with a similar proficiency in their L1 and L2. It is not clear whether the same control mechanisms and/or neural signatures would be observed in bilinguals with different levels of proficiency in their L1 and L2 or with distinct immersive profiles. Thus, studies testing bilinguals with different proficiency levels or L2 immersion, are needed to shed further light on this important matter.

Third, our language switching task is restricted to the laboratory setting. This may not accurately reflect the real-world language control abilities of bilinguals. For instance, recently proposed models of language control in bilinguals (e.g., the ACH) suggests that control mechanisms are flexible and depend on the context at hand. Thus, a critical avenue for future research is the design and implementation of more ecological paradigms able to capture language control "in the wild". This will provide a more complete picture of how bilinguals manage their languages in natural situations.

It is important to note that these limitations do not diminish the significance of our findings, but rather highlight areas for future research to expand upon and further validate our results.

5.5 Concluding remarks

Overall, this dissertation provides new insights into how highly proficient bilinguals handle language control during speech production, and how neuroplasticity processes can preserve this ability even in the presence of a brain tumor. Firstly, our findings show that healthy bilinguals with a similar proficiency in their L1 and L2 use a common language-independent control mechanism to manage lexico-semantic access during language switching. This mechanism, supported by right parieto-frontal alpha oscillations (8-13 Hz), is responsible for controlling the selection of lexical items during language switching through a process of (dis)inhibition. From a theoretical standpoint, these results contribute to our understanding of the oscillatory signatures supporting language control in bilinguals, an aspect that has been poorly studied in the field. However, they also have potential applications in clinical settings as they can inform the development of neurolinguistic interventions for bilingual patients with language disorders. Additionally, these findings may also have an impact on educational methods aimed at improving second language learning through the use of neurofeedback or brain stimulation protocols.

Secondly, this thesis shows that bilingual patients harboring brain tumors in critical brain nodes involved in language control put in place neuroplasticity mechanisms that enable them to preserve this ability, albeit at higher cognitive and neural costs. This functional compensation is supported by alpha oscillations (8-13 Hz) which mediate the additional recruitment of a wider bilateral network. These results have important clinical implications for improving intra-operative mapping of language control abilities in bilingual patients.

Thirdly, this thesis demonstrates that the switching task implemented in our experiments is reliable and can be used to investigate language control processes in different language pairs. The finding that both groups of highly proficient bilinguals (Spanish/Basque and Italian/Friulian) showed similar switch costs at the behavioral level suggests that the task is sensitive in tapping into the language control process. This makes our task potentially useful in neurosurgery, as it could be used to identify the functional boundaries of language processing areas and improve surgical outcomes.

Last but not least, the results of the brain stimulation study support the idea that the left AG and the pMTG play distinct causal roles in controlling different aspects of linguistic processing, particularly when cognitive and neural demands are high. This highlights the importance of using a multimethod approach which allows us to cross-validate findings and gain a more comprehensive understanding of brain function.

Taken together, these findings provide new insights into the spectro-temporal and spatial signatures supporting language control in the bilingual brain and the potential reshaping of these patterns in the presence of brain damage. Beyond theoretical implications, this dissertation provides valuable clinical information to plan surgical strategies tailored to patients' linguistic profiles. Such a strategy can improve tumor resection during surgeries, while fully preserving language control abilities in bilingual individuals and, consequently, their quality of life.

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APPENDIX

Appendix A: Chapter 4:

Appendix D1: Linguistic profiles

Table 11 Questionary used to evaluate language history and daily use patterns in Italian/Friulian bilingual participants. This questionary is adopted from (Gatignol et al., 2009).

Family history questionary
What is the family's country of origin?
Age you were first exposed to Friulian?
What languages does your mother speak?
What languages does your father speak?
Are you right or left-handed?
Do you speak other languages than Italian or Friulian?
Part II: Education background
Now, what language do you use?
At home, to your spouse, living companion?
At home to your children?
At home, to your colleagues at work?
At home, to other relatives?
To your friends
How would you rate your speaking ability in L1/ L2?
Rate yourself according to the following categories
L1: very good, somewhat good, somewhat poor, very poor
L2: very good, somewhat good, somewhat poor, very poor
How would you rate your reading ability in L1/L2?
L1: very good, somewhat good, somewhat poor, very poor
L2: very good, somewhat good, somewhat poor, very poor
How would you rate your writing ability in L1/L2?
L1: very good, somewhat good, somewhat poor very poor
L2: very good, somewhat good, somewhat poor, very poor
How would you rate your comprehension ability in L1/L2?
L1: very good, somewhat good, somewhat poor, very poor
L2: very good, somewhat good, somewhat poor, very poor
Which language do you feel more comfortable speaking?
Which language do you speak when you're really tired?

When you are angry?

When you’re incredibly happy?

Which language do you use in simple arithmetic (counting, adding, multiplying, etc?)

Which language do you speak when you’re really tired?

When you are angry?

When you’re incredibly happy?

Which language do you use in simple arithmetic (counting, adding, multiplying, etc?)

All subjects administered the questionnaire in Italian. (A) Self-rating on a 5-point scale (1–5: very good–very poor)

Appendix A22: stimulation parameters by participant

Table 12 Stimulation parameters (averages of all participants)

ID	Motor coordinates	Vertex coordinates	Motor threshold
1	-59 -20 60	2 -32 82	37
2	-47 -15 70	-1 -9 79	43
3	-45 -20 70	-1 -20 74	45
4	-48 -16 65	-4 -10 80	48
5	-35 -8 73	0 -18 72	42
6	-50 -20 67	-2 10 76	39
7	-47 -9 68	1 -5 79	41
8	-48 -17 68	1 -25 83	33
9	-63 -8 68	-2 -5 78	40
10	-58 -16 68	-3 11 81	46
11	-49 -16 67	-5 -25 80	33
12	-45 -19 71	-1 14 81	38
13	-45 -17 70	-4 -8 80	40
14	-50 -13 66	0 -11 81	41
15	-49 -15 70	3 -7 80	38
16	-49 -10 68	0 7 73	35