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CROSS CEREBRO-CEREBELLAR LANGUAGE LATERALIZATION IN LESIONED AND UNLESIONED BRAINS: A FUNCTIONAL AND STRUCTURAL NEUROIMAGING STUDY

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What horrifies me most is the idea of being useless: well-educated, brilliantly promising, and fading out into an indifferent middle age.

-- Sylvia Plath

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LIST OF ABBREVIATION

BOLD blood oxygenation level-dependent

LI lateralization indices

fMRI functional magnetic resonance imaging

MRI magnetic resonance imaging

mSTG middle superior temporal gyrus

aSTG anterior superior temporal gyrus

pSTG posterior superior temporal gyrus

AVS auditory ventral stream

ADS auditory dorsal stream

DTI diffusion tensor imaging

IFG inferior frontal gyrus

FA fractional anisotropy

CCT cerebro-cerebellar tract

AF arcuate fasciculus

STG superior temporal gyrus

MDLF middle longitudinal fasciculus

SMG supramarginal gyrus

MTG middle temporal gyrus

ROI region of interest

WLI weighted lateralization index

AveLI average lateralization index

VG verb generation

SA semantic association task

PA phonological association task

TE echo time

TR repetition time

FOV field-of-view

AG angular gyrus

DW diffusion-weighted

1.1. SUMMARY

One of the more advanced cognitive abilities that sets humans apart from other species is language: the ability to have a complex system of sounds associated with distinct meanings to express thoughts and emotions. Neuroimaging studies in healthy subjects and those with lesions have shown that language functions depend on the functional integration of several specialized regions in the temporal and frontal lobes, i.e., Wernicke's and Broca's areas respectively (Purves et al., 2004). These regions are located in the left cerebral hemisphere in the temporal lobe and in the frontal lobe, respectively, for about 95% of right-handers, and about 70% of left-handers (Griggs, 2010). As is evident, language functions are unequally represented in the two cerebral hemispheres, i.e., are lateralized. Especially in individuals that are right-handed, specific language functions such as comprehension, vocabulary and grammar are typically lateralized to the left hemisphere (Taylor & Taylor, 1990). Speech production is also left-lateralized in most right-handed people, while it may be atypical, i.e., bilateral, or right-lateralized, in a fraction of the left-handed population (Beaumont, 2008). Interestingly, language localization and lateralization are not limited to the cortical i.e., the supratentorial regions. The cerebellum (which is part of the infratentorial brain) contralateral to the ‘language-dominant’ hemisphere has been shown to participate in language regulation in terms of verbal fluency, grammar, language error corrections as well as writing skills (Starowicz-Filip et al., 2017).

Deficits in language processing acutely affect quality of life due to which clinicians make every effort to identify and preserve cortical areas involved in its comprehension and production. Consequently, understanding language lateralization becomes especially important in neurosurgical procedures, where there is a need to map language functions in patients for the purpose of sparing eloquent regions of the brain. This is particularly relevant in procedures that involve surgical removal of cerebral tumors. While there has been evidence for crossed cerebro-cerebellar language lateralization related to language dominance in brain tumor patients (Hubrich-Ungureanu et al., 2002), clinical neuroimaging studies assessing hemispheric language lateralization mainly focus only on the supratentorial brain. But a recent study provided evidence that these activations can act as an additional feature to assess language dominance with both typical and atypical language lateralization (Méndez Orellana et al., 2015). This study opened avenues to test whether language activation in the cerebellum can guide the determination of language dominance because cerebellar activation is generally undisturbed by the tumor localized in the presumed cortical language areas. Additionally, these crossed activations are of a special interest in language recovery and rehabilitation in patients suffering from aphasia, as they may help visualize the reorganization of language and reveal atypical language lateralization which in turn may help define the viability of life-saving lobectomies in these patients (Mendez Orellana et al., 2012). This can prove especially useful in cases where the tumor makes lateralization determination difficult.

So far, only covert verb generation paradigms have been used to study these activations (FitzGerald et al., 1997; Hubrich-Ungureanu et al., 2002). These tasks are difficult to monitor in the scanner and may be challenging for the patients to perform especially if their tumor is affecting the language regions. Hence, on top of the traditional verb generation paradigm, we use semantic and phonological association tasks as alternative, easier language paradigms to establish the occurrence of the crossed activations in subjects that had difficulty performing the former. These activations could be observed not only in healthy subjects, but also in patients with brain tumors across all three tasks despite the cerebral lesion affecting blood oxygenation level-dependent (BOLD) signal (Thakkar et al., 2022). This was true for a cohort with both left- and right-handed patients with a brain tumor as well as left- and right-handed healthy controls included from the patients' peers and matched for age, gender, and educational level.

Once the presence of these activations was established in patients, we evaluated and compared different indices used for lateralization determination (lateralization indices or LI) based on BOLD activations in both the cortex and the cerebellum. While the current method used in the clinic is fairly robust, there are certain challenges to implementing it. It was shown that LI calculations based on fMRI depend on the statistical confidence threshold that is used to determine the number of activated voxels (Ruff et al., 2008). Hence, we use a threshold-independent LI calculation technique (Branco, et al., 2006; Suarez et al., 2009) and compared them with manual expertise to check their reliability in the clinic since these methods are still being explored in experimental settings and require further clinical confirmations.

As a further validation to the functional 'crosstalk' that seems to be occurring between the language-dominant cortex and the cerebellum while performing language tasks, we also study the anatomical white matter connection between these two structures that specifically recruits the cerebellum to contribute to verbal processing functions in both healthy subjects and subjects with cerebral tumor. To further understand language lateralization in these cohorts, we established the presence of these language-related white matter tracts.

In a nutshell, this thesis uses functional data as well as tractography data collected from healthy subjects and patients with brain tumors to investigate the functional and anatomical mechanisms of both typical and atypical crossed cerebro-cerebellar activations. We discovered that the semantic and phonological association tasks were consistent with the verb generation task and hence may prove to be useful tools in presurgical crossed cerebro-cerebellar language lateralization determination. We also observed that threshold-independent LI techniques are not consistently congruent with manually assigned lateralization. Additionally, it was observed that a good portion of both of our cohorts demonstrated white matter tracts that connect the contralateral cerebellum to major language regions individually. The findings from this project shed light on their mechanisms in lesioned brains as well as the importance of the cerebellum in the identification of typical and atypical language lateralization in patients with brain tumors or otherwise.

1.2. RESUMEN

Una de las habilidades cognitivas más avanzadas que distingue a los humanos de otras especies es el lenguaje: la capacidad de tener un sistema complejo de sonidos asociados con distintos significados para expresar pensamientos y emociones. Los estudios de neuroimagen en sujetos sanos y con lesiones han demostrado que las funciones del lenguaje dependen de la integración funcional de varias regiones especializadas en los lóbulos temporal y frontal, es decir, las áreas de Wernicke y Broca respectivamente (Purves et al., 2004). Estas regiones están ubicadas en el hemisferio cerebral izquierdo en el lóbulo temporal y en el lóbulo frontal, respectivamente, para alrededor del 95% de las personas diestras y alrededor del 70% de las personas zurdas (Griggs, 2010). Como es evidente, las funciones del lenguaje están desigualmente representadas en los dos hemisferios cerebrales, es decir, están lateralizadas. Especialmente en personas diestras, las funciones específicas del lenguaje, como la comprensión, el vocabulario y la gramática, suelen estar lateralizadas hacia el hemisferio izquierdo (Taylor & Taylor, 1990). La producción del habla también está lateralizada a la izquierda en la mayoría de las personas diestras, mientras que puede ser atípica, es decir, bilateral o lateralizada a la derecha, en una fracción de la población zurda (Beaumont, 2008). Curiosamente, la localización y lateralización del lenguaje no se limitan a las regiones corticales, es decir, supratentoriales. Se ha demostrado que el cerebelo (que es parte del cerebro infratentorial) contralateral al hemisferio 'dominante del lenguaje' participa en la regulación del lenguaje en términos de fluidez verbal, gramática, corrección de errores del lenguaje y habilidades de escritura (Starowicz-Filip et al., 2017).

Las deficiencias en el procesamiento del lenguaje afectan de manera aguda la calidad de vida, por lo que el personal clínico hace todo lo posible para identificar y preservar las áreas corticales involucradas en su comprensión y producción. En consecuencia, comprender la lateralización del lenguaje se vuelve especialmente importante en los procedimientos neuroquirúrgicos, donde existe la necesidad de mapear las funciones del lenguaje en los pacientes con el fin de preservar regiones elocuentes del cerebro. Esto es particularmente relevante en procedimientos que implican la extirpación quirúrgica de tumores cerebrales. Si bien ha habido evidencia de lateralización cruzada del lenguaje cerebro-cerebeloso relacionada con el dominio del lenguaje en pacientes con tumores cerebrales (Hubrich-Ungureanu et al., 2002), los estudios clínicos de neuroimagen que evalúan la lateralización del lenguaje hemisférico se enfocan principalmente solo en el cerebro supratentorial. Sin embargo, un estudio reciente proporcionó evidencia de que estas activaciones pueden actuar como una característica adicional para evaluar el dominio del lenguaje con lateralización del lenguaje tanto típica como atípica (Méndez Orellana et al., 2015). Este estudio abrió vías para probar si la activación del lenguaje en el cerebelo puede guiar la determinación del dominio del lenguaje porque la activación del cerebelo generalmente no se ve afectada por el tumor localizado en las presuntas áreas corticales del lenguaje. Además, estas activaciones cruzadas son de especial interés en la recuperación y rehabilitación del lenguaje en pacientes con afasia, ya que pueden ayudar a visualizar la reorganización del lenguaje y revelar una lateralización atípica del lenguaje que, a su vez, puede ayudar a definir la viabilidad de lobectomías salvadoras en estos pacientes. pacientes (Méndez Orellana et al., 2012). Esto puede resultar especialmente útil en los casos en que el tumor dificulte la determinación de la lateralización.

Hasta ahora, solo se han utilizado paradigmas de generación de verbos encubiertos para estudiar estas activaciones (FitzGerald et al., 1997; Hubrich-Ungureanu et al., 2002). Estas tareas son difíciles de monitorear en el escáner y pueden ser un desafío para los pacientes, especialmente si su tumor afecta las regiones del lenguaje. Por lo tanto, además del paradigma tradicional de generación de verbos, utilizamos tareas de asociación semántica y fonológica como paradigmas lingüísticos alternativos y más fáciles para establecer la ocurrencia de las activaciones cruzadas en sujetos que tenían dificultad para realizar las primeras. Estas activaciones podrían observarse no solo en sujetos sanos, sino también en pacientes con tumores cerebrales en las tres tareas a pesar de que la lesión cerebral afecta la señal dependiente del nivel de oxígeno en sangre (BOLD) (Thakkar et al., 2022). Esto fue cierto para una cohorte con pacientes diestros y zurdos con un tumor cerebral, así como controles sanos diestros y zurdos incluidos de los compañeros de los pacientes y emparejados por edad, sexo y nivel educativo.

Una vez establecida la presencia de estas activaciones en los pacientes, evaluamos y comparamos diferentes índices utilizados para la determinación de lateralización (LI) basados en activaciones BOLD tanto en la corteza como en el cerebelo. Si bien el método actual utilizado en la clínica es bastante sólido, existen ciertos desafíos para implementarlo. Se demostró que los cálculos de LI en fMRI dependen del umbral de confianza estadística que se utiliza para determinar el número de vóxeles activados (Ruff et al., 2008). Por lo tanto, usamos una técnica de cálculo de LI independiente del umbral (Branco, et al., 2006; Suarez et al., 2009) y los comparamos con experiencia manual para verificar su confiabilidad en la clínica, ya que estos métodos aún se están explorando en entornos experimentales. y requieren más confirmaciones clínicas.

Como una validación adicional de la activación funcional cruzada que parece estar ocurriendo entre la corteza dominante del lenguaje y el cerebelo mientras se realizan tareas de lenguaje, también estudiamos la conexión anatómica de la materia blanca entre estas dos estructuras que reclutan específicamente al cerebelo para contribuir a las funciones de procesamiento verbal tanto en sujetos sanos como en sujetos con tumor cerebral. Para comprender mejor la lateralización del lenguaje en estas cohortes, establecimos la presencia de estos tractos de materia blanca relacionados con el lenguaje.

En pocas palabras, esta tesis utiliza datos funcionales, así como datos de tractografía recopilados de sujetos sanos y pacientes con tumores cerebrales para investigar los mecanismos anatómicos y funcionales de las activaciones cerebro-cerebelosas cruzadas típicas y atípicas. Descubrimos que las tareas de asociación semántica y fonológica eran consistentes con la tarea de generación de verbos y, por lo tanto, pueden resultar herramientas útiles en la determinación de la lateralización del lenguaje cerebro-cerebeloso cruzado prequirúrgico. También observamos que las técnicas de LI independientes de umbral no son consistentemente congruentes con la lateralización asignada manualmente. Además, se observó que una buena parte de nuestras dos cohortes demostraron tractos de materia blanca que conectan el cerebelo contralateral con las principales regiones del lenguaje individualmente. Los hallazgos de este proyecto arrojan luz sobre sus mecanismos en los cerebros lesionados, así como sobre la importancia del cerebelo en la identificación de la lateralización típica y atípica del lenguaje en pacientes con tumores cerebrales o no.

2. INTRODUCTION

2.1. Cross Cerebro-Cerebellar Language Lateralization

2.1.1. <u>Language: Localization and Lateralization</u>

Wernicke-Lichtheim-Geschwind model

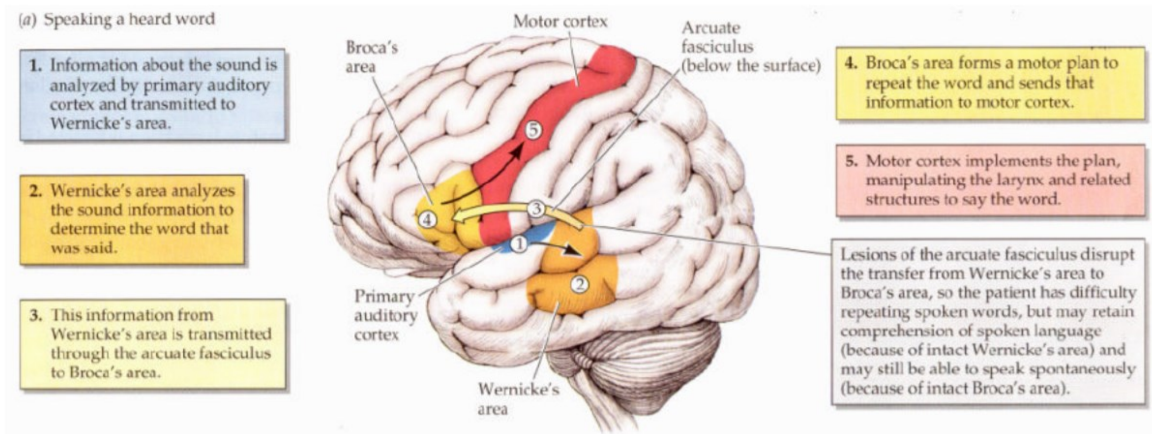

Figure 1. *A schematic of the Wernicke-Lichteim-Geschwind model describing the traditional understanding of language processing. Figure taken from Kreutzer et al., 2011.*

Language is a complex system that is spread across a large part of the cerebral cortex (Beaumont, 2008). Historically, to understand language processing in the brain, we have relied on the Wernicke-Lichteim-Geschwind model (Figure 1) (Geschwind, 1965; Lichteim, 1885; Wernicke, 1974). Based mainly on cases of individuals with brain damage presenting a variety of language related disorders, the model suggests the existence of a specialized word reception and perception center called the Wernicke's area located in the left temporoparietal junction and a word production center called the Broca's area located in the left inferior frontal gyrus, with the former projecting to the latter. However, the advancements in neuroimaging, especially magnetic resonance imaging (MRI), contributed to our current understanding of language functions as this model was shown to be imperfect (Anderson et al., 1999; DeWitt & Rauschecker, 2013; Dronkers et al., 2000; Dronkers et al., 2004; Mesulam et al., 2015; Poeppel et al., 2012; Vignolo et al., 1986).

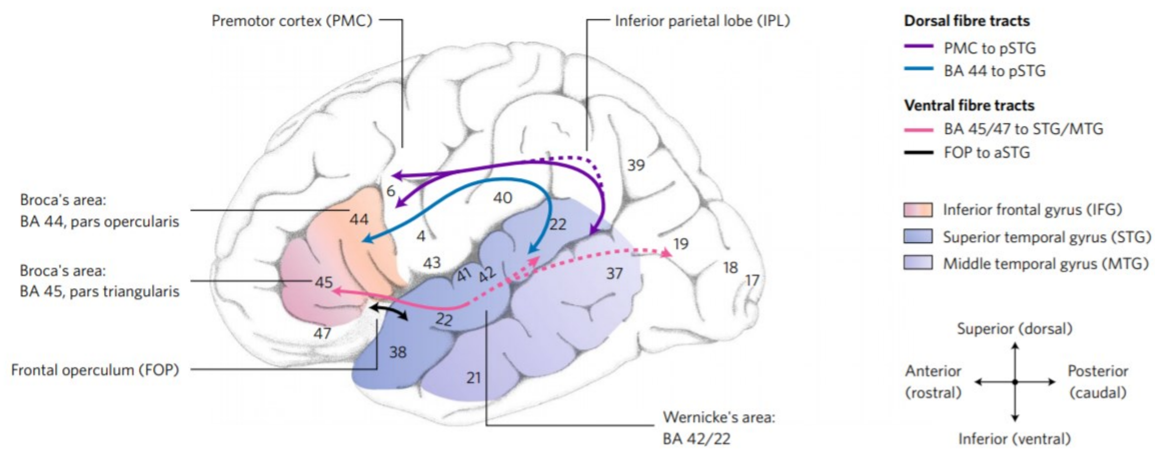

Figure 2. *Structural connectivity between language regions. A schematic, condensed view of language-relevant brain regions and fibre tracts in the left hemisphere. The dorsal fibre tracts connecting the posterior temporal cortex (pSTG) with the frontal cortex involves the superior longitudinal fascicle and the arcuate fascicle. There are two streams with different termination points: one in the dorsal premotor cortex (PMC) (purple tract), and the other in BA 44 (blue tract). The ventral fibre tracts connecting the frontal cortex to the temporal cortex also consists of two streams: one going from BA 45 to the temporal, parietal and occipital cortex, involving the inferior fronto-occipital fascicle (pink tract); and the other going from the frontal operculum (FOP) to the anterior superior temporal gyrus (aSTG), involving the uncinate fascicle (dark grey tract). Taken directly from Friederici et al., 2017.*

Currently, much of our knowledge of the neural correlates of language in humans comes from MRI studies. Anatomically speaking, the primary auditory region, known as the Heschl's gyrus (Brodmann Area 41 and 42 (Yousry et al., 1997)), has two distinct and bilateral auditory fields: the anterior primary auditory field (hR), and the posterior primary auditory field (hA1) (Da Costa et al., 2011; Langers & van Dijk, 2012; Striem-Amit et al., 2011; Woods et al., 2010). The former field projects to the middle-anterior superior temporal gyrus (mSTG-aSTG), and the latter to posterior superior temporal gyrus (pSTG) and the planum temporale (Gourévitch et al., 2008; Guéguin et al., 2007; Poliva et al., 2015). Studies have shown the planum temporale to be one of the most asymmetric regions in the brain, with this area being up to ten times larger in the left cerebral hemisphere than the right in most cases (Becker et al., 2002). Incidentally, the left planum temporale coincides with what was thought to be Wernicke's area (Dehaene, 1999) i.e. left Brodmann Area 22 (J. J. Eggermont, 2014; Karbe et al., 1995).

From the STG, studies in primates have demonstrated that auditory/language processing flows via two main pathways: the Auditory Ventral Stream (AVS) and the Auditory Dorsal Stream (ADS) (Cohen et al., 2004; Lewis & Van Essen, 2000; Perrodin et al., 2011; Petkov et al., 2008; Roberts et al., 2007; Romanski et al., 2005; Seltzer & Pandya, 1984; Tsunada et al., 2011). Furthermore, diffusion tensor imaging techniques (DTI) have shown that this ventral-dorsal white matter pathways involved in communication is homologous in humans and monkeys (Catani et al., 2005; Frey et al., 2008; Makris et al., 2009; Menjot de Champfleur et al., 2013; Saur et al., 2008; Turken & Dronkers, 2011). Particularly in humans (Figure 2), AVS consists of the aSTG projecting to the middle temporal gyrus and the temporal pole in the anterior temporal lobe and from there to the inferior frontal gyrus (IFG). Meanwhile, ADS consists of the pSTG projecting to sylvian parietal-temporal junction and the inferior parietal lobule from where projections reached the dorsolateral prefrontal and premotor cortices as well as the language-dominant IFG. The language-dominant IFG coincides with Brodmann Areas 44 and 45 (usually the left), also known as Broca's area (Dronkers et al., 2007).

Functionally speaking, AVS is colloquially known as the ‘what’ stream, and is involved in sound recognition, and speech comprehension and functions mostly bilaterally. On the other hand, ADS is known as the ‘where’ stream and contributes in sound localization, and particularly in humans (usually left-lateralized), speech production and repetition, associating lip movements with corresponding sounds, as well as phonological working and long-term memory (Gow Jr, 2012; Hickok & Poeppel, 2007).

In terms of lateralization, most of the afore-mentioned statistics have considered solely right-handed individuals. Lateralization of function is especially relevant in context of language and is heavily associated with handedness (Beaumont, 2008). This idea first emerged when it was observed that lesions in the right hemisphere rarely produced speech disorders in right-handed individuals, but frequently did so in left-handed persons (Heilman & Valenstein, 2010). Eventually, large studies from the Satz group concluded that 95% of the recruited right-handed individuals have language lateralized to the left, 5% to the right, and none bilaterally. Alternatively, 76% of the recruited left-handers had bilateral speech representation, 24% left-lateralized, while none of them had speech lateralized to the right (Carter et al., 1980; Satz, 1979). In another study that used the Wada test (Wada, 1949) and published around the same time, 96% of the healthy right-handed participants showed left-lateralized speech, 4% showed right-lateralized and none showed bilateral speech. In 70% of healthy left-handed participants speech was left-lateralized while the rest of the 30% had right-lateralized and bilateral speech equally (Rasmussen & Milner, 1975). It can be seen that language lateralization statistics differed dramatically for left-handed individuals in these studies. This could be due to differences in the methods used to infer speech representation, in criteria for bilateral representation, and/or in handedness classification (Beaumont, 2008).

Thus, knowing an individual's handedness, especially in the clinical contexts, is not enough to deduce their language lateralization as more precise models are needed for the same. This becomes relevant especially because handedness may affect the severity of aphasia and the possibility of recovery brought in by lesions limited to a single hemisphere (Beaumont, 2008). There are some particularly clinical methods that are currently in place to determine language lateralization in a patient which is discussed in Section 2.2. These methods, as will be elaborated upon, also require increased robustness. The solution to this may lie in the following section.

2.1.2. <u>Language and the Cerebellum</u>

Traditionally, the cerebellum has been associated with regulation of motor functions including visuo-motor coordination and muscle tone (Starowicz-Filip et al., 2017). One of the first studies to establish an association with cerebellar functioning to semantic and phonological abilities was a case report of a patient with a vascular injury in the right cerebellar hemisphere. In spite of demonstrating high levels of conversional skills, the patient was unable to generate verbs in response to a noun or to notice and correct his

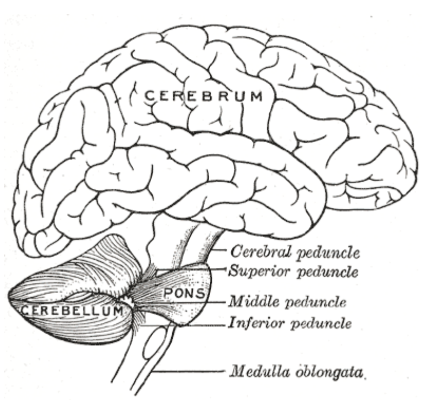

Figure 3. *Structural overview of the supratentorial and infratentorial brain. Taken from Gray, 1918.*

numerous language mistakes (Fiez et al., 1992). In a subsequent verbal fluency study (Leggio et al., 1995), participants with cerebellar damage, especially in the right hemisphere, showed lower levels of semantic and phonological fluency as compared to control subjects as well as a cohort of subjects with brain lesions in other regions. Relatively recently, verbal fluency impairment and slower name retrieval was observed in patients with neurodegenerative cerebellar injuries (Stoodley & Schmahmann, 2009). Transcranial magnetic stimulation of the right cerebellar hemisphere in healthy subjects also caused a decrease in cognitive flexibility (Arasanz et al., 2012).

Other clinical studies have observed subjects with cerebellar damage displaying symptoms of language dysfunction like anomy, agrammatism and dysprosody (Schmahmann & Sherman, 1998). The first study to demonstrate cerebellum's role in grammar processing was a case study of a subject with focal vascular injury to the right cerebellar hemisphere whose speech patterns consisted of omissions of syllables, and temporary grammatical violations like missing or replacing essential nouns (Silveri et al., 1994). This role was further consolidated through other subsequent studies (Fabbro et al., 2000; Gasparini et al., 1999; Justus, 2004; Zettin et al., 1997). The cerebellum was also shown to contribute to identification and control of potential linguistic mistakes before verbal utterance (Friederici, 2006; Hoeks et al., 2004; Schmahmann, 2004).

Cerebellar deficits have also been shown to cause serious language disorders. Although controversial (Frank et al., 2008; Richter et al., 2005), several cases of cerebellar aphasia have been reported (Baillieux et al., 2010; Bartczak et al., 2011; De Smet et al., 2011; Karacı et al., 2008). Furthermore, cerebellar dysfunction has been associated with writing disorder, also known as agraphia (De Smet et al., 2011; Frings et al., 2010; Peter Mariën et al., 2009, 2013; Silveri et al., 1997) and lowered reading abilities (Moretti et al., 2002). Anomalies in the structure of the cerebellum have also been associated with dyslexia (Brown et al., 2001; Nicolson & Fawcett, 1999).

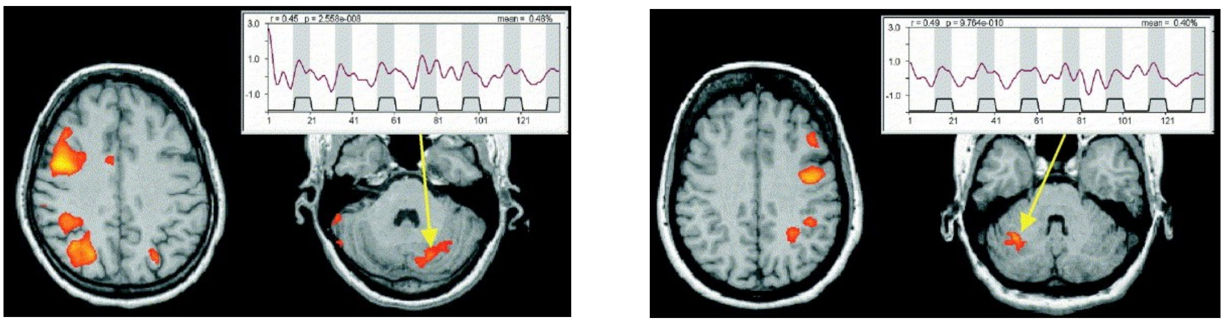

Figure 4. *Results from Hubrich-Ungureanu et al., 2002 show the involvement of the contralateral cerebellum for the first time as healthy subjects performed a silent verbal fluency task in an MR scanner. For right-handed participants, activations were observed in the left cortex and the right cerebellum simultaneously. Vice versa was observed in left-handed participants.*

In fact, several developmental dyslexia theories have been based on the functional deficit of cerebro-cerebellar connections (Baillieux et al., 2009; Starowicz-Filip et al., 2017). A covert verbal fluency fMRI study also demonstrated the importance of these connections (Hubrich-Ungureanu et al., 2002). Unsurprisingly, right-handed individuals showed cerebral activations in the left frontoparietal regions. At the same time, significant contralateral activations were observed in the cerebellum (Figure 4). Similar, but reversed i.e., atypical activations were observed in left-handed participants as well. This study helped elucidate cerebellum's major contralateral role in language regulation to that of the cerebral cortex, i.e., the cross cerebro-cerebellar activations. This was already confirmed by a previous case study of a patient with right cerebellar damage displaying symptoms impaired spontaneous speech, fragmented utterances, and deficient word generation, reading and writing skills while maintaining naming and phonological skills, and repetition (Mariën et al., 1996). These symptoms were analogous to those resulting due to damage to the left frontal regions despite absence of any cortical injuries in the patient. This led to the notion of the 'lateralized linguistic cerebellum' i.e. a strong engagement of the contralateral cerebellum in language functions (Mariën et al., 2001). Over the years, several studies, mainly fMRI, have validated both typical and atypical (i.e. bilateral) crossed cerebro-cerebellar patterns (Cook et al., 2004; Fabbro et al., 2000; Frank et al., 2010; Jansen et al., 2005; Méndez Orellana et al., 2015; Murdoch & Whelan, 2007) further consolidating their role as a possible key to improved clinical interventions.

2.1.3. White Matter Tracts in Language

Before the advent of clinical studies in language impairment due to cerebellar deficit, the involvement of the cerebellum in language was brought upon by the discovery of its neural connections to the frontal cortical areas, notably the Broca's area (Leiner et al., 1991). Bidirectional pathways, i.e., the cerebral peduncles, exist between each cerebral hemisphere and its contralateral cerebellar hemisphere (Figure 5). The ascending pathway (the fronto-ponto-cerebellar projections) starts from the frontal regions and projects to the pontine nuclei in the brainstem (the corticopontine tract) from where it projects to the lateral portions of cerebellar hemispheres (the pontocerebellar tract) via mossy fibers. The ascending pathway also consists of another tract that projects from the cortex to the red nucleus, then to the medial olivary nucleus ending in the cerebellum. The descending pathway (the cerebello-thalamic-frontal projections) projects to the anterior nucleus in the thalamus from the dentate nucleus in the cerebellum through the cerebellothalamic tract. From there, it projects to the contralateral areas of the frontal lobe via the thalamocortical pathway (Karavasilis et al., 2019; Ramnani, 2006; Schmahmann, 1996; Schmahmann & Pandya, 2008). Fractional anisotropy (FA) in the superior cerebellar peduncle was found to be significantly reduced in subjects with postoperative cerebellar mutism syndrome as compared to participants with normal language functioning (McEvoy et al., 2016) suggesting serious implications in case of cerebro-cerebellar tract (CCT) damage.

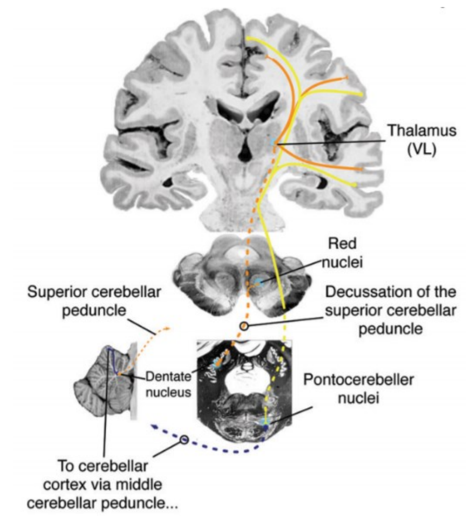

Figure 5. *Cortico-cerebello-cortical loops. Descending cortico-ponto-cerebellar fibers target cerebellar nuclei in the pons. These nuclei send crossed projections to the cerebellar cortex via the middle cerebellar peduncle. Purkinje neurons of the cerebellar cortex project to subcortical cerebellar nuclei (the largest of which is the dentate nucleus). These nuclei send crossed projections to the ventrolateral (VL) nucleus of the thalamus, which then project to the cortex. Dotted projections indicate approximate pathway of the tract through the brainstem. Taken directly from Dick et al., 2013.*

Within the supratentorial brain, tracts connecting the major cortical language regions as described in Section 2.1.1., known as the arcuate fasciculus (AF) and its associate tract has been characterized (Catani et al., 2005; Frey et al., 2008). The AF connects the Broca’s and Wernicke’s areas through the ADS. The white mater tracts of the AVS pathway were also discovered through (Frey et al., 2008; Parker et al., 2005). Along with the direct tract connecting Broca’s and Wernicke’s area, an indirect tract, via the uncinate fasciculus and the superior temporal gyrus (STG) has also been observed (Parker et al., 2005). In the same study, 9 out of 12 participants had connections from the STG to prefrontal Brodmann Areas 6 and 8, and then to the left ventral posterior intraparietal sulcus. The latter were found to be a part of the middle longitudinal fasciculus (MDLF). Furthermore, it was discovered that the anterior supramarginal gyrus (SMG) projects to the posterior SMG which is connected to the angular gyrus (Lee et al., 2007) contributing to the merger of phonological knowledge to semantic knowledge (Geva et al., 2011).

Notably, properties of these white matter tracts seem to have ramifications in regulation of language functions. Structurally, the AF has been shown to be left-lateralized regardless of handedness or language lateralization (Vernooij et al., 2007). However, males have been shown to have clear AF laterality, while females have shown bilateral symmetry in AF (Catani et al., 2007). The same study observed that AF symmetry across hemispheres was associated with higher performance in memorizing words using semantic associations. It has been shown, that especially in right-handed individuals, direct white matter tracts from Wernicke’s area project to the middle temporal gyrus (MTG), the STG, and Brodmann Area 40 in the left hemisphere, but only to the latter in the right (Parker et al., 2005). Moreover, all right-handed participants have been shown to have connections between MTG and IFG in the left hemisphere, but only a fraction of the participants had that connection, diminished in size, in the right (Glasser & Rilling, 2008).

The study of white matter tracts and their laterality can contribute to our understanding of both the prognosis and recovery of aphasia (Geva et al., 2011). For example, it has been shown that hemispheric symmetry in these tracts can lead to better recovery, with right hemispheric tracts able to compensate for loss of function in the left hemisphere (Catani & Mesulam, 2008). But, bearing in mind the importance of both the cerebellum and the CCT, it would be remiss to not consider their contribution to the above cause. CCT abnormality has already been shown in reading-impaired children. Poor readers had greater FA as compared to typical readers (Fernandez et al., 2016). This study not only suggested the importance of discrete cerebellar functions but also of projections from the anterior cerebellum having a regulatory effect on the language pathway. Specifically, in case of patients with tumors, albeit post-surgery, subjects showed decreased perfusion within the cerebellar grey matter contralateral to the supratentorial lesion, but an increase in FA in the cerebral white matter that declined with time (Patay et al., 2014).

Considering the literature at hand, it is only reasonable to assume the role of the cerebellum, the CCT, especially their lateralization, to be irrefutable not only in language function but also in its rehabilitation. Furthermore, these discoveries were afforded thanks to modern functional and structural neuroimaging techniques due to which this study proposes to combine both these essential modalities to achieve its objectives.

2.2. Lateralization Indices

According to an estimate (Patel et al., 2019), there are around 330.000 new incidences of brain and other central nervous system cancer each year, with the rates increasing about 17% in the last 25 years. In Chile alone, there are 550 new cases

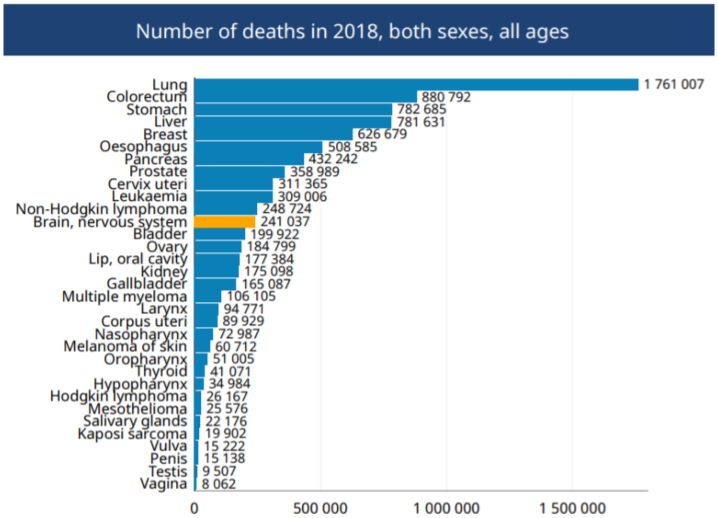

Figure 6. *Total number of deaths in women and men due to different categories of cancer in 2018. Number of deaths due to brain and nervous system cancer is highlighted in yellow. Data taken from Globocon 2018 (International Association of Cancer Registries, International Agency for Research on Cancer).*

every year, 14% more than 25 years ago. The National Cancer Institute of the United States of America (https://www.cancer.gov/) states that one of the treatment options suggested and often performed for most kinds of tumors is neurosurgery, since removing tumor tissue helps decrease pressure of the tumor on nearby regions of the brain. In such cases, quality of life becomes a crucial aspect in the decision to undergo such an intervention. Language production and comprehension is a substantial part of postoperative quality of life due to which the potential of losing language function postoperatively may preclude surgical resection of a tumor (Ruff et al., 2008). To that account, preoperative assessment of language localization becomes crucial in surgical resection planning and for evaluating the possibilities of cortical mapping while the patient is awake. fMRI techniques, being non-

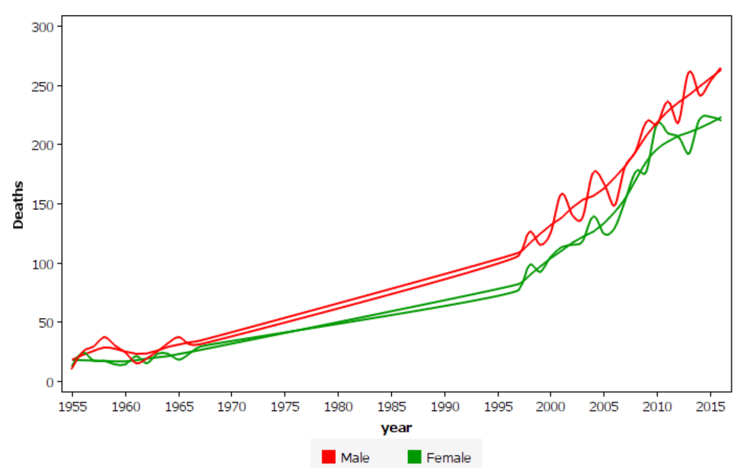

Figure 7. *Mortality from brain and central nervous system tumors in Chile across years. Data is for patients of all ages. Taken from the website of the International Agency for Research on Cancer on 6th March 2020.*

invasive and replicable, have proven to be a useful tool to establish interactions between functional language lateralization in the brain and the tumor (Gapen et al., 2016; Maldjian et al., 1997; Moritz & Haughton, 2003; Roux et al., 2003) making it possible for the surgeon to adjust their approach. Although intraoperative cortical mapping using electrocorticography remains the gold standard for localizing language in patients with tumor, numerous studies have shown significant association between that technique and fMRI (Benson et al., 1999; Brannen et al., 2001; Ojemann, 1993; Petrovich et al., 2004). Furthermore, using fMRI would not only reduce total surgical time, but also prove useful in cases of intraoperative failure due to seizures or problems with anesthesia.

In the MR scanner, language lateralization is determined by the language laterality index (LI) first proposed in 1995 (Desmond et al., 1995). LI is widely used to determine presurgical language dominance for patients with brain tumor (Gaillard et al., 2004; Lehéricy et al., 2000; Rutten et al., 2002; Woermann et al., 2003) and is calculated by the number of active voxels in each cerebral hemisphere as follows:

$$\frac{L_a - R_a}{L_a + R_a}$$

Here, L_a and R_a are the number of activated voxels in the left and right hemispheres, respectively. Activations are classified as left-lateralized for positive values, right-lateralized for negative values, or bilateral for LI values usually between or equal to –0.1 and +0.1 (Binder et al., 2008; Holland et al., 2007; D. Lee et al., 2008; Szaflarski et al., 2006; Tillema et al., 2008). Closer the value to 0, the more symmetrical is the language representation. While this method is fairly robust, there are certain challenges to implementing it. It was shown that LI calculations in fMRI depend on the statistical confidence threshold that is used to determine the number of activated voxels in each hemisphere (Ruff et al., 2008). The choice of region of interest (ROI) also changes the value of LI (Seghier, 2008).

Considering these shortcomings, several studies have attempted to improve upon techniques that guide clinicians in identification of language lateralization. For example, several threshold-independent methods have been recommended in current literature. In one of these methods, activated voxels are determined by comparing the integrated T-score weighted distributions of the positively correlated voxels between the left and right hemisphere ROIs (Branco et al., 2006; Suarez et al., 2009). A weighing function (T-score^2) is applied to bins of voxels with positive T-score values for each hemisphere separately and then integrated (area under the curve of the plotted function). The weighted LI (WLI) is then determined by applying the following ratio:

$$\frac{L_{HA} - R_{HA}}{L_{HA} + R_{HA}}$$

Here, L_{HA} and R_{HA} represent the area under the weighted distribution curve for the left hemisphere and the right hemisphere respectively. Activations are classified as left-lateralized for values ranging from 0.1 to 1.0, right-lateralized for values between –0.1 and –1.0, and symmetric for values between or equal to -0.1 and 0.1 (Suarez et al., 2009).

Likewise, other similar threshold independent methods that use different weighing functions have also gained traction. The Average Lateralized Index (AveLI)

(Matsuo et al., 2012) is another threshold independent method where voxel t-values are sorted by magnitude from activation in the bilateral ROIs. These sorted t-values are plotted onto the horizontal axis such that the top t-value falls on the rightmost end and the median value is at the center. The area under the curve would represent the AveLI value. The formula for this index is as follows:

$$\frac{\sum \frac{L_t - R_t}{L_t + R_t}}{V_n}$$

Here, L_t and R_t are the summations of voxel t-values at and above the threshold in the left and right ROIs, respectively. V_n is the total number of voxels with positive t-values within the ROIs.

These methods are still being explored in experimental settings and require further clinical confirmations.

Another approach to tackling the challenge of lateralization determination in lesioned brains may be to take into account activations that remain uncontaminated by tumor presence altogether. Taking in consideration the crossed cerebro-cerebellar activations, it was shown that lateralizations obtained using language BOLD activations in the cortex were highly significantly correlated to those obtained from contralateral

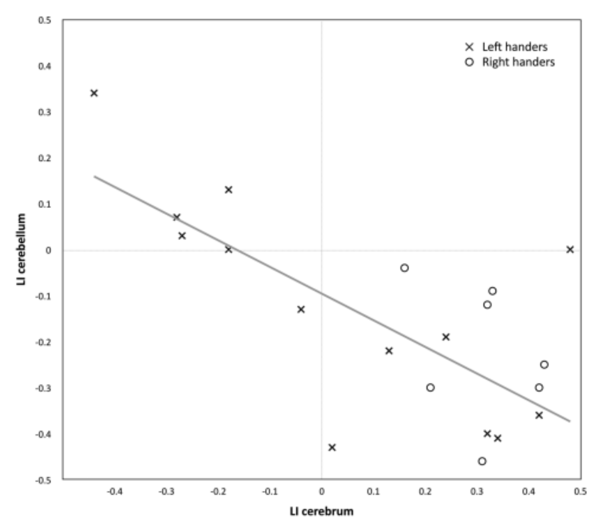

Figure 8. *Scatterplot of the healthy participants' lateralization indices of the cortex vs. the cerebellum as shown in Méndez-Orellana et al., 2015.*

activations in the cerebellum (Figure 8) (Méndez Orellana et al., 2015). This opens the possibilities of exploring LIs beyond the information from cortical regions.

2.3. Alternative Language Paradigms as Presurgical Tools for Inducing Crossed Cerebro-Cerebellar Language Activations in Brain Tumor Patients

So far, studies investigating crossed cerebro-cerebellar language activations in healthy participants as well as in patients with brain lesions have focused mainly on covert language production paradigms, i.e., word production tasks such as the verb generation (VG) task (Fitzgerald et al., 1997; Hubrich-Ungureanu et al., 2002). There may be two major disadvantages to the VG paradigm: First, the task may be too difficult to perform for patients with aphasia due to the presence of a lesion in or near their language areas. Second, as a covert paradigm, the task cannot be monitored. Hence, it is difficult to ascertain whether the patients performed the task correctly and whether the resultant language activation is reliable. Some alternative language paradigms are the semantic and phonological association decision tasks (SA and PA), which are easier to perform for patients with severe aphasia (Méndez-Orellana et al., 2012) and allow the monitoring of respective task performance because subjects are expected to respond with button-presses. Although these tasks have been implemented in clinical fMRI (Dym et al., 2011), the crossed cerebro-cerebellar language activations associated with this task remain unclear. In the present study, we aim to investigate whether crossed cerebro-cerebellar language lateralization activations previously reported with the verb generation fMRI task can also be visualized with semantic and phonological tasks.

2.4. Conclusion and Direction

So far, in addition to describing the anatomy, structural connections and functions of language in the human cortex, the thesis introduction looks into the significance of the cerebellum for language regulation. Furthermore, this text also delved into the dynamics of language lateralization, both structural and functional. It was demonstrated with compelling evidence that the cerebellum as well as the cerebro-cerebellar white matter tracts participate in this functional lateralization of language. The need to use alternative, response-based paradigms was also established. Finally, we propose it is crucial to bring all these conclusions in the context of determining language lateralization for patients across a wide age group with brain tumors in the clinic.

In a nutshell, using fMRI and DTI, this thesis offers to explore mechanisms of language lateralization and its relation to the cerebellum, across varying degrees of handedness across all ages in brain tumor patients compared to healthy controls. One of the goals of the study was to work closely with clinicians to evaluate the efficacy of considering cerebellar activations using threshold-independent LI methods. Clinically, the discovery of a relevant cerebellar white matter feature is expected to aid lateralization determination in patients for timesaving, less cumbersome presurgical evaluation procedures.

3. OBJECTIVES

The main objective of the thesis project is as follows:

To establish the role, or lack thereof, of the cerebellum and the structural pathway between cortical language regions and the cerebellum, in functional language lateralization.

The specific objectives of the proposal are as follows:

- Objective 1: To establish the involvement of the cerebellum in phonological and semantic language regulation in subjects with tumors as well as healthy subjects.
- Objective 2: To evaluate and compare different LI methods that use BOLD information from the cortico-cerebellar activations for determining language lateralization and compare their efficacies to manual clinical expertise.
- Objective 3: Using tractography, to observably establish this pathway in both healthy and lesioned brains.

4. HYPOTHESES

The main hypothesis of the thesis project is as follows:

The cerebellum and the cross cerebro-cerebellar tracts play an important role both in the lateralization and processing of language in healthy subjects as well as patients with brain tumors.

In accordance with the hypothesis, the following experimental predictions are expected:

- Cross cerebro-cerebellar BOLD activity will be observed for semantic and phonological association tasks in control as well as tumor patient cohorts
- Threshold-independent LI methods will be more effective if not comparable to manual lateralization determination with cerebellar activations.
- White matter pathways connecting the contralateral cerebellum to the main regions involved in language processing are observed for both control and tumor patient cohort.

5. METHODOLOGY

5.1. Participants

Patients with brain tumors at different sites (n = 71, age range 19 – 78 years, mean age = 45.29 years, standard deviation of age = 15.17, females = 38, left-handed = 3, all patients had primary tumors except 6 subjects who had metastasis. For more details on location, type, and grade of tumor lesions, refer to the table in Appendix I) were recruited from outpatient clinics of the departments of neurosurgery at the Hospital Clínico Pontificia Universidad Católica de Chile, Hospital Complejo Asistencial Dr. Sótero Del Río as well as Hospital Barros Luco Trudeau. Healthy subjects matched on average with patients by age, gender, education level and handedness (n = 24, age range 20 – 73 years, mean age = 41.4 years, standard deviation of age = 15.95, females = 13, left-handed = 8) were recruited from the included patients' peers. At the time of the patient's enrollment in the study, their peers were informed of the possibility to participate in the study as a healthy control. If they are interested in participating, they informed of their interest through a return form or upon the patient's next outpatient visit. Subjects were recruited under FONDECYT Initiation into Research Study Nº 111150429. This study was approved by the scientific ethical committee at the School of Medicine, Pontificia Universidad Católica de Chile (Approval N° 15-302). All subjects signed an informed consent form before the imaging.

The inclusion criteria for these subjects were age (18 to 75 years), monolingualism, right- or left-handedness as assessed by the Edinburgh Handedness Test (Oldfield, 1971), and a balanced body mass to fit into the magnetic resonance machine. On the other hand, subjects were excluded if they had any of the following conditions: severe developmental dyslexia, severe hearing deficits, severe perceptual visual disorders, severe motor disabilities (inability to make independent transfers), recent psychiatric history, or contraindications for magnetic resonance imaging. Patients were also tested for any language impairment using a full battery of language tasks that included the test to measure spontaneous speech standardized for Chilean individuals (Méndez-Orellana et al., 2019), the Token Test (Renzi and Faglioni, 1978), and the full Spanish version of the Dutch Linguistic Intraoperative Protocol (Witte et al., 2015). For more clarity, Appendix II may be referred to view samples of these language tests.

5.2. Instrumentation

The experiment and all the corresponding scanning were performed in the Philips Ingenia 3T MRI system installed in the Department of Radiology (https://www.usa.philips.com/), at Pontificia Universidad Católica de Chile. An axial three-dimensional (3D) fast-field echo T1-weighted image (echo time (TE)/repetition time (TR) 4/8.5ms, flip angle 8 degrees, matrix 240 x 240, field-of-view (FOV) 24.0x24.0 cm) with an effective slice thickness of 1.0 mm was acquired for anatomical registration purposes. Functional scans were acquired using a gradient echo-planar imaging pulse sequence (TE/TR 35/3500 ms, flip angle 90 degrees, matrix 96 x 96, FOV 23.0 - 23.0 cm) with a slice thickness of 3.0 mm (no gap). Total acquisition time was 5:14 min, which included 5 of dummy scans that will be discarded from further analysis. Diffusion-weighted technique, diffusion tensor imaging (DTI) was used to acquire white matter information (b-value = 800 s/mm^2, slice thickness = 2.0 mm, slices = 32, diffusion-weighted directions = 32).

5.3. fMRI Language Paradigms

The main aim of the present work was to evaluate the potential of the VG, SA, and PA tasks to assess crossed cerebro-cerebellar language activations in patients with brain lesions affecting the BOLD fMRI signal in cortical regions. We also compared these tasks to the standard verbal fluency VG task for the same capacity. Therefore, the experiment consisted of all the three tasks performed by all the recruited participants. The order of each task was randomly presented to each participant. The covert VG task is the most commonly used task to evaluate language lateralization in brain tumor patients (Hubrich-Ungureanu et al., 2002; Smits et al., 2006; Méndez-Orellana et al., 2015). Participants were instructed to think of a verb related to nouns that were presented through an auditory cue. The control condition for this task was the subjects listening to repeated high (2000 Hz) and low (400 Hz) tones. Each experimental block lasted 27s and had 9 nouns. Each block was repeated 5 times with a respective control block (Figure 9). For the SA task (Figure 10 (above)), each stimulus block consisted of 6 pairs of nouns that were either semantically related or unrelated (3 and 3 pairs, respectively, randomly arranged). The control condition for this task was the subjects listening to 3 tones (500 Hz) and 3 bursts of noise (Brownian noise), the order of which was also random. The subjects were instructed to press the response button upon hearing a pair of words that were semantically related and not respond when the words were not related semantically. In the control condition, subjects had to press the button when they heard Brownian noise. The PA task (Figure 10 (below)) was identical to its semantic counterpart, except the task consisted of pairs of words that did or did not rhyme. For both tasks, each block was 21s long and repeated 6 times with a respective control block. Subjects were presented these tasks using the Presentation software (Neurobehavioral Systems) which also registered their performance for the two button-press tasks. Prior to the actual scanning sessions, participants trained for each task on a laptop device with the Presentation software but using a different set of stimuli word pairs. Association tasks that the subjects were unable to perform above chance level in the practice session were not included in the actual scanning session. While the order of the tasks was randomized for each participant, this order remained identical between their training and actual scanning sessions.

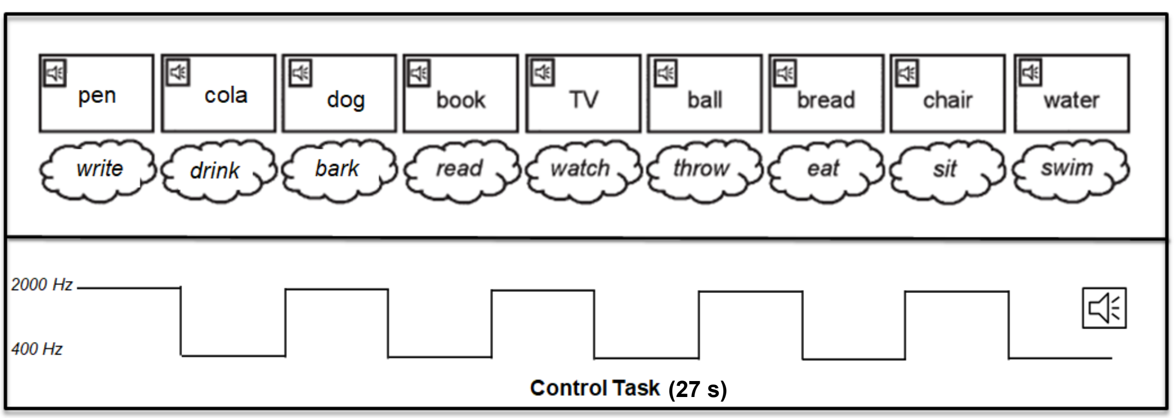

Figure 9. *Representation of each experimental block of the verb generation task followed by its control block. The above block was repeated 5 times for each subject with its control task. Each experimental block was 27s long. It is important to note that the nouns in the figure are only representative. The actual noun cues used in the experiment were in Spanish given it being the first language of all participants.*

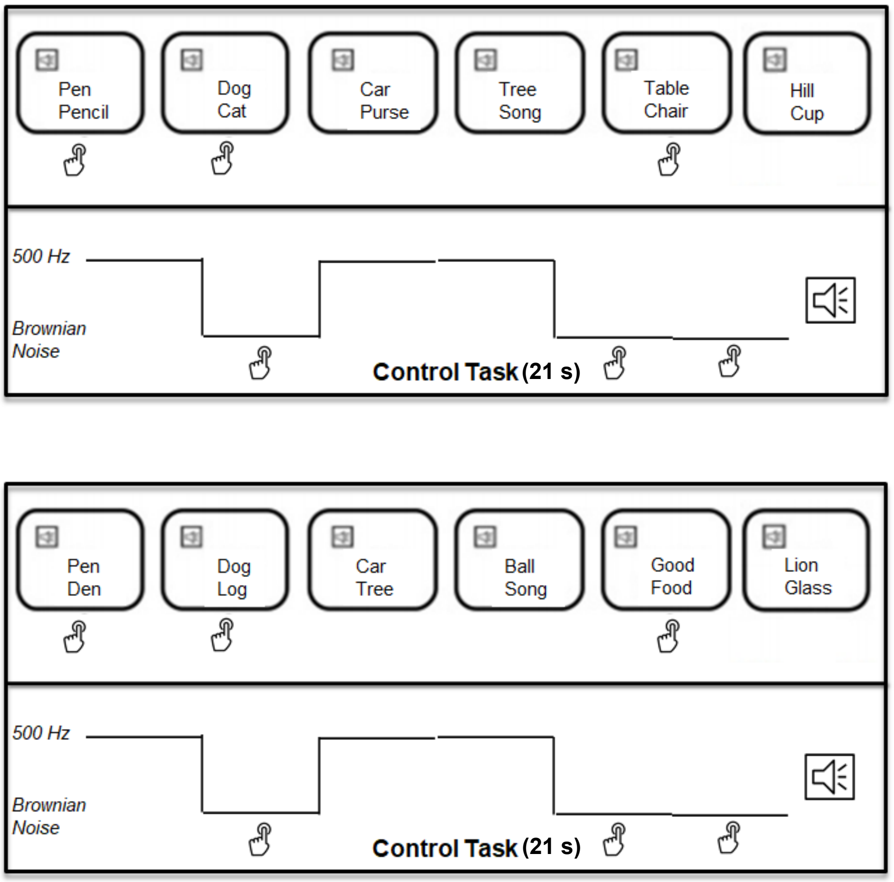

Figure 10. *Representation of each experimental block of the semantic (above) and phonological (below) association tasks followed by their control block. The above block was repeated 6 times for each subject with its control task. Each experimental block was 21s long. It is important to note that the semantic and phonological word pairs in the figure are only representative. The actual cues used in the experiment were in Spanish given it being the first language of all participants.*

The data collection process for each subject consisted of an initial anatomical scan, followed by functional scans where subjects performed these tasks, finally followed by the DTI sequence.

5.4. Data Processing

5.4.1. <u>BOLD Analysis</u>

In-scanner performance on tasks was evaluated for all subjects based on the signal detection theory (making use of the number of hits, misses, false alarm, and correct rejections). Subjects reached at least 95% accuracy rate in their responses.

Functional imaging data was preprocessed using SPM8 software (Wellcome Centre for Human Imaging) using an established protocol in MathWorks MATLAB version 2021a (Méndez-Orellana et al., 2015). For healthy subjects, the first step was to realign all the images for motion correction. First, multiple regressors are estimated to represent how different other slices are from the first slice. Then once aligned, these images are "resliced" into voxels again as per the voxel positions of the first slice. Next, these functional images are co-registered to the high-resolution anatomical image. Then, images are segmented to differentiate between grey matter, white matter and cerebrospinal fluid followed by the normalization of all images to the standard MNI space. Finally, images are smoothed.

The pipeline was adjusted to clinical requirements for tumor patients considering the presence of lesions that contaminate BOLD signal and interfere with preprocessing algorithms. The first step was to manually realign all functional images for motion correction. This was done by manually setting the origin of the 3D space at the anterior commissure for each subject visualized using the SPM user interface. Then, using the SPM function Realign: Estimate, multiple regressors were estimated to represent how different slices are from the first slice i.e., the reference slice. These parameters (shown as the matrix with elements p) will be used for the 2nd level analysis as confounds in the general linear model. Next, these functional images are co-registered to their respective high-resolution anatomical image. Finally, the images were smoothed using a gaussian kernel. Segmentation was not performed as the tumor may be wrongly classified as being part of healthy brain tissue. Normalization was not performed as the lesion may be stretched to incorrect proportions or location.

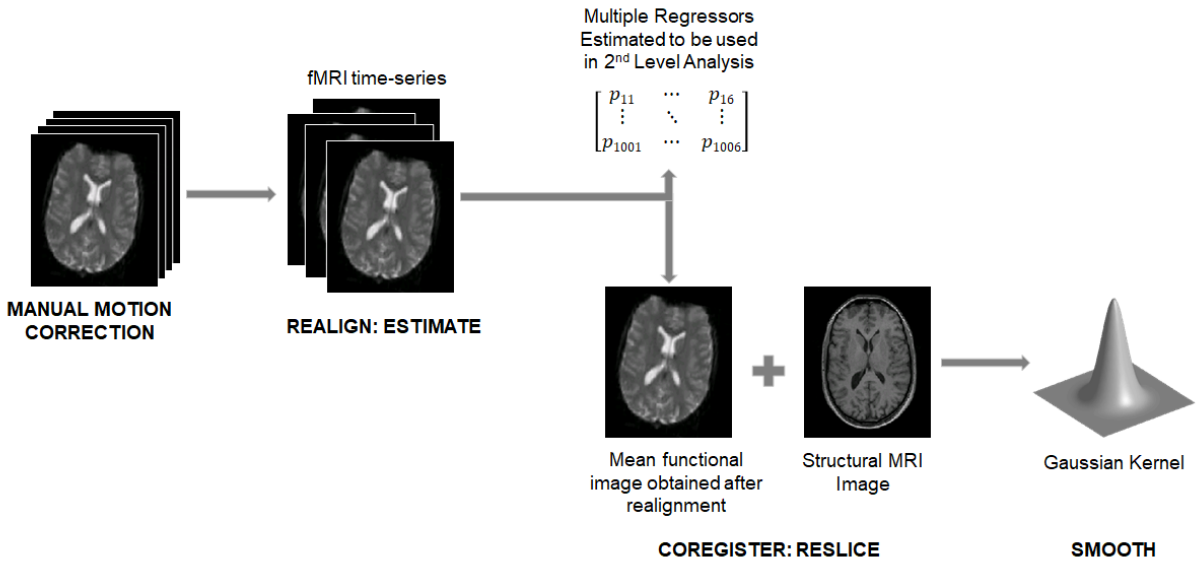

Figure 11. *BOLD preprocessing pipeline adjusted for patients with brain tumors.*

A general linear model was used to generate statistical activation maps to visualize activation related to task performance. First step is to define the conditions of the task and assign which functional slices belong to which condition i.e., task or rest. Based on that, a model is generated using maximum likelihood which is then translated to statistical maps that contain active voxels based on a threshold that may be related to the task effect. This is repeated for each task. The detailed preprocessing pipeline is described in Figure 11. Individual t-contrast images, thresholded individually at a minimum t-value of 2, were assessed qualitatively by a neuroradiologist blinded to the language tasks, and handedness of the participants. Language activation was evaluated for the IFG, STG, MTG, supplementary motor area, AG, SMG, and the cerebellum. These are the same language areas as those quantitatively assessed in healthy participants in Mendez Orellana et al (2015).

5.4.2. Lateralization Determination

For each region, activation was categorized as left-lateralized, right-lateralized, bilateral, or no activation by the neuroradiologist. Based on the activation in the cortical regions mentioned above, an overall assessment of supratentorial language representation was made. This was obtained independently for all three tasks. Subjects who could perform only one out of the three tasks (n = 1 for healthy subjects, n = 2 for patients) were excluded before all statistical analyses. To validate the ratings of the neuroradiologist, a second neuroradiologist assigned laterality to each subject while also being blinded to the language tasks and handedness of the participants. It was observed that the activations were clear, and the two sets of ratings only differed for cortical activations from VG and PA tasks for the same subject and for cerebellar activations from the SA task for another subject. The 3 ratings that differed were then decided upon by the thesis director based on clinical recommendations before data analyses. No incongruences were found in ratings of healthy subjects between manual raters as observed through a case-by-case comparison.

The above-described manual rating process was distinct from obtaining the automatized LI values using T-Maps. For the threshold-independent methods, the creators of WLI and AveLI were approached for algorithms for their respective techniques. They provided us with the MATLAB code that was used for calculations for their respective indices used in our analysis.

5.4.3. <u>Statistical Analysis</u>

All statistical analyses were performed using SPSS statistical software, version 26 (IBM Corporation).

Finally, to test the agreement of lateralization patterns of the two new tasks with the VG task, a Cohen's kappa test was performed between the VG cerebral activation and those of the other two tasks individually. The same was done for their cerebellar activation. Next, we also encoded cerebrocerebellar activation as crossed or not for each task for each participant. Cerebro-cerebellar activation was categorized as crossed for cases where activation in the cortex and cerebellum was in the opposite hemispheres, or when cerebellar activation was unilateral for bilateral cortical activation. All other cases were categorized as uncrossed. Then, a separate Cohen's kappa test was performed between the VG task and SA task, as well as the VG task with PA task with the new crossed/uncrossed variables. Patients that showed no BOLD activation in either the cortex or the cerebellum ($n = 14$ for VG with SA, $n = 13$ for VG with PA) were excluded from this particular analysis. All remaining healthy subjects showed activations in the cortex and the cerebellum.

Furthermore, to test the significance of the occurrence of the crossed cerebro-cerebellar activation, we also performed a two-tailed McNemar test with $\alpha = 0.05$ between the cerebral and cerebellar activation for each task; cases with no activations in either the cerebellum or the cortex were excluded. These analyses were all for manual lateralization assignments.

Similar statistical analyses were used to compare threshold-independent LIs with manually observed lateralization. We used Pearson's *r* to test contralaterality between the LI values obtained from the cortex and the cerebellum for each threshold-independent method separately. Finally, we used Cohen's kappa test between manual lateralization and WLI and AveLI individually for all tasks across both groups.

5.4.4. Tractography Analysis

The analyses to obtain tractography results were carried out independently from all BOLD analyses. All DTI analyses were conducted using the ExploreDTI MATLAB Toolbox (Leemans et al., 2009). DTI data was preprocessed following a standard pipeline (Figure 12) established for clinical work of the thesis director courtesy of the ProVIDI Lab at Utrecht University, The Netherlands.

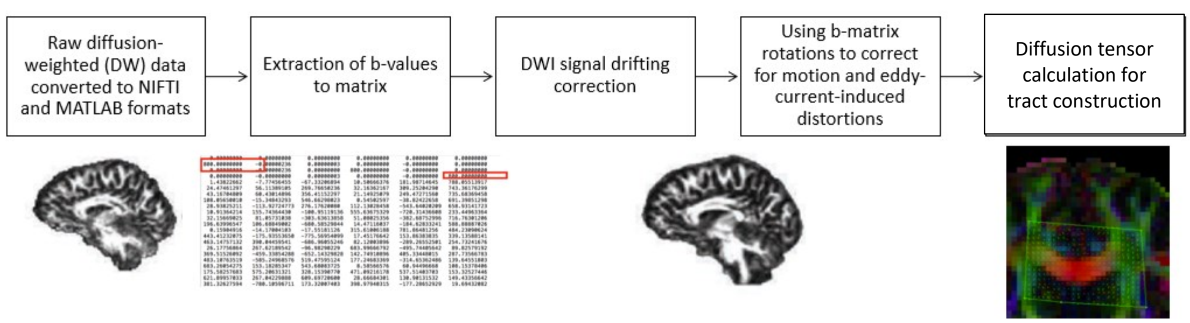

Figure 12. *DTI preprocessing pipeline. Raw diffusion-weighted (DW) data was converted to NIFTI (.nii) and MATLAB (.mat) formats from which b-values were extracted to a b-matrix. Images were then corrected for drifting by using b-matrix rotations to correct for motion and eddy-current-induced distortions. Then, diffusion tensor model was calculated which would be used for tract construction.*

Once preprocessing was performed, the quality of the data becomes more apparent. The biggest challenge for our dataset was the zebra effect (Tournier et al.,

2011) where, due to a higher level of motion inside the scanner, the scanned slices fail to align with each other correctly. This creates a wobbly-looking image (Figure 13) where one can see alternatively misaligned slices like the stripes of a zebra (hence the name). This effect was exacerbated by the fact that the DTI protocol was at the end of the entire experimental paradigm and participants, especially patients, started growing uncomfortable, and as a result moving more inside the scanner. Due to the discomfort, patients even chose to opt out of the paradigm altogether.

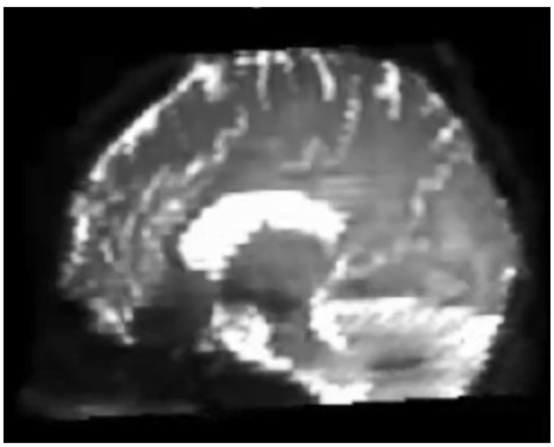

Figure 13. *The Zebra Effect. Subjects were excluded from final tract construction due to this noise. The image shows a sagittal slice of one of the healthy subjects excluded from final analysis.*

Hence, for the tractography analysis, the subject population consisted of fewer participants (for healthy participants: *n* = 14, age range 20 – 70 years, mean age = 42.4 years, standard deviation of age = 15.68, females = 6, left-handed = 4; and for patients: *n* = 22, age range 20 – 78 years, mean age = 44.3 years, standard deviation of age = 17.03, females = 11, left-handed = 0, 7 subjects with tumor in the right hemisphere).

Once this cohort was retained for analysis, white matter tracts could be constructed using the deterministic streamline approach. With the help of neuroradiologists, ROIs corresponding to pars opercularis and pars triangularis (which together make up the region associated with language in the IFG), and one corresponding to the SMG and AG were defined on 2 axial planes. ROIs for the cerebellum were also defined. This was done for each individual healthy subject and patient for both hemispheres. These particular ROIs were chosen for this proof-of-concept analysis because they are part of the dorsal stream of language processing.

The tracts were then constructed using tracking parameters (FA range for seed point selection = 0.15 – 1, minimum FA to allow tracking = 0.15, maximum tracking angle = 70°, step size = 1 mm, fiber length range = 1 – 500 mm, seed point super-sampling factor = 2x2x2) from Keser et al., 2015 and Oh et al., 2016 which have already demonstrated reconstructed white matter tracts to the cerebellum from the cortex, but in healthy subjects.

6. RESULTS

6.1. Crossed Cerebro-Cerebellar Language Activations

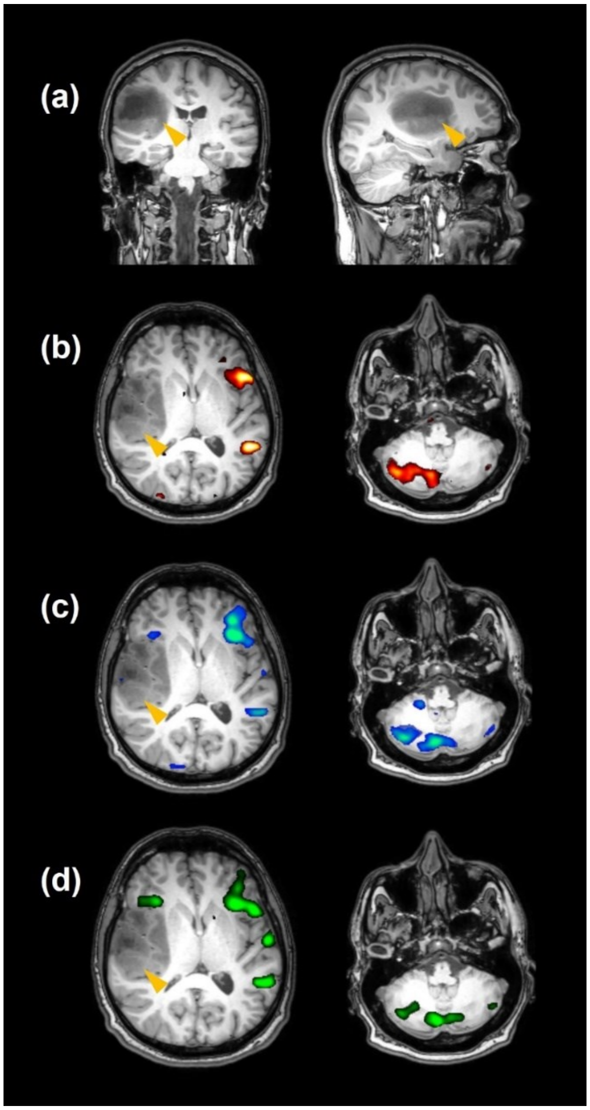

Figure 14. *Language-related BOLD activations for the VG, SA, and PA Tasks. The (a) shows the coronal and sagittal anatomical views of one of the participants (male, 31 years old, right-handed). The yellow arrow points at the tumor in the cortex. The lesion was a grade II primary tumor in the fronto-parieto-insular region in the right hemisphere. The tumor was classified as a diffuse astrocytoma. The subject was assigned left laterality in the cortex for all three tasks and right laterality for the cerebellum for all three tasks. The three figures below are the two radial views of the same subjects with cortical and cerebellar BOLD activations (threshold range set to 6 - 2.5 in MRIcron (McCausland Center for Brain Imaging)) from the three tasks overlayed on the anatomical image. Figures (b), (c), and (d) show task-activated voxels for VG (red), SA (blue) and PA (green) tasks respectively. The tumor in the radial view is marked by a yellow arrow. All figures are in the radiological convention.*

Figure 14 shows an anatomical image in coronal and sagittal views of one of the tumor patients from the study. The tumor can be seen covering large area of parietal lobe reaching to the frontal lobe (yellow arrow). Task-activated voxels for each task are overlaid on the anatomical image as shown in the figure. Red is activation during the VG task, blue is SA and green is PA.

A preliminary glance at the data revealed that 17 out of 23 healthy subjects showed identically lateralized cerebral and cerebellar activations in at least 2 tasks, out

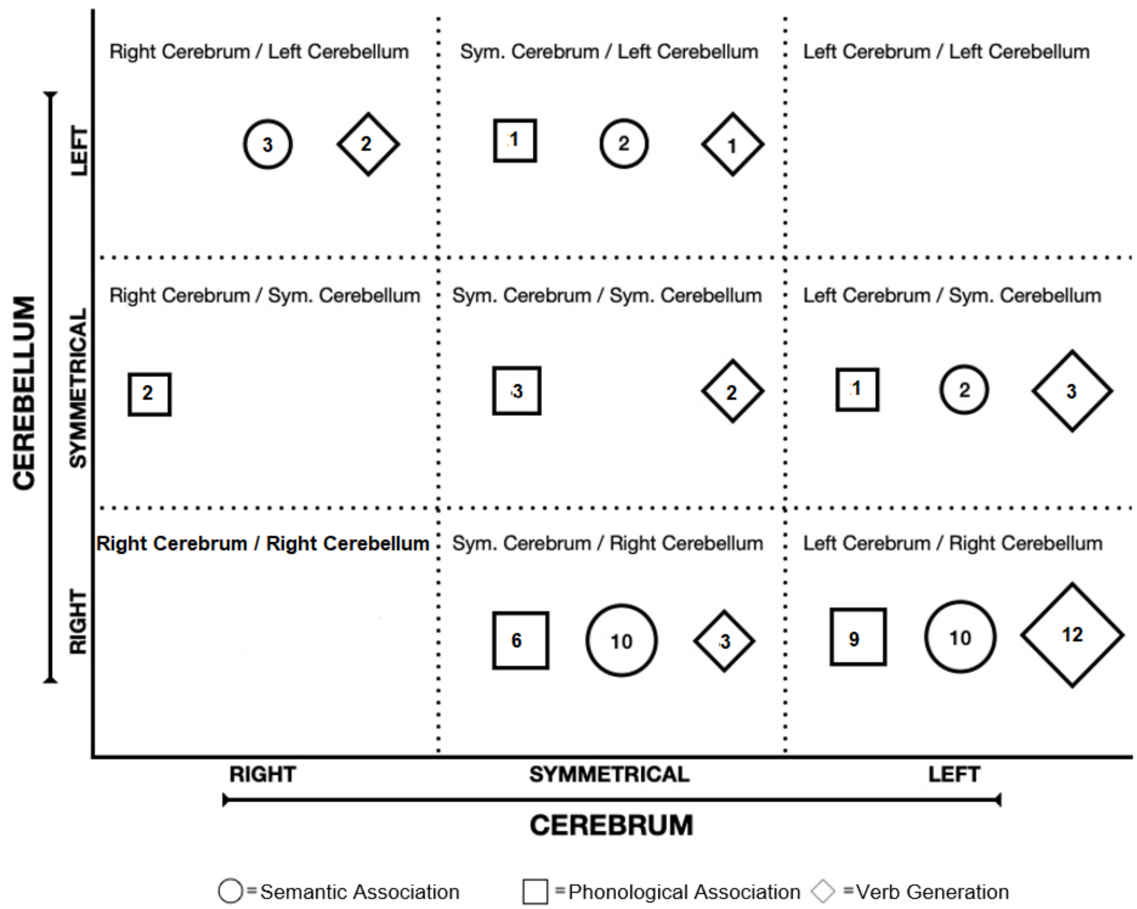

Figure 15. *Cerebro-cerebellar language representation in healthy participants.*

of which 5 subjects showed identically lateralized cerebral and cerebellar activations in all 3 tasks. As for whether tasks identified crossed or uncrossed activations, 21 subjects showed crossed activations in at least 2 tasks, out of which 12 subjects showed crossed activations in all 3 tasks (Figure 15).

As for the patient cohort, 59 out of the 69 remaining subjects had identically lateralized cerebral and cerebellar activations for at least 2 tasks, out of which rest 29 of them had identically lateralized cerebral and cerebellar activations for all three tasks. Notably, 47 subjects showed crossed cerebro-cerebellar activations in at least 2 tasks, out of which 28 showed crossed activations in all 3 tasks (Figure16). Out of the 69 subjects, 50 subjects had their tumor located in the left hemisphere. 31 of these 50 subjects showed crossed activations in at least two tasks, with 15 in all three. 18 subjects had lesions in their right hemisphere, and 15 of these subjects showed the crossed cerebro-cerebellar activations in at least 2 tasks. Out of them, 11 subjects showed crossed activations in all three tasks. Crossed activations for the one subject who had tumors in both hemispheres were observed in 2 (SA and PA) tasks.

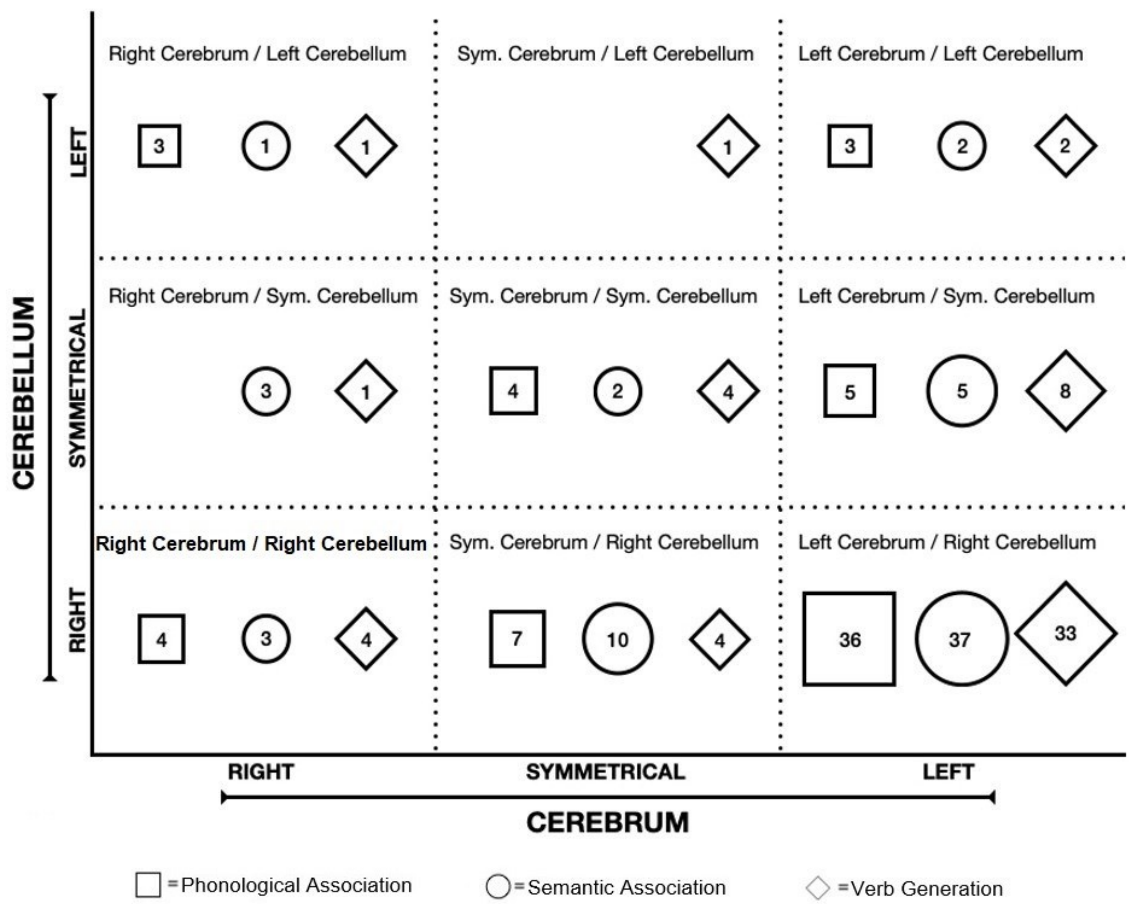

Figure 16. *Cerebro-cerebellar language representations in patients*

In terms of inter-task reliability of the two new tasks with the VG task, Cohen's Kappa revealed the following results in healthy subjects. The Kappa value for SA cerebral activations and their VG counterparts was .196 with a standard error of .199. It is interesting to note that while the P-value was .22, 13 out of 23 subjects showed identical cortical activations between the two tasks. For the same task, reliability in cerebellar activations was statistically significant with a P-value of .003. The Kappa value was .42 with a standard error of .16. For the agreement in occurrence of crossed/uncrossed cerebro-cerebellar activations between VG and SA tasks, the Kappa value was .18 with a standard error of .23. While the P-value was .33, 17 out of 22 valid cases for this analysis showed agreement in whether the cerebro-cerebellar activations were crossed or uncrossed between the two tasks.

For the PA task and its agreement with VG in healthy subjects, for cerebral activations, the Kappa value was .23 with a standard error of .19 and a P-value of .14. Yet, 13 out of 23 subjects showed agreement in cortical activation lateralization between these two tasks. For cerebellar activations, the Kappa value was .32 with a standard error of .17 and a P-value of .037. For whether activations were crossed or uncrossed, the Kappa value was .15 with a standard error of .27 and a P-value of .467. Yet, 17 out of 22 valid subjects showed an agreement in whether they had crossed or uncrossed activations between the VG and PA tasks.

On the other hand, for agreement in lateralization of activations in the patient cohort revealed the following. For cortical activations in SA and VG, the Kappa value was .63 with a standard error of .099 and a P-value < .001. For reliability in cerebellar activations for these 2 tasks, the Kappa value was .17 with a standard error of .096 and a P-value of .04. As for their crossed/uncrossed agreement, the Kappa value was .25 with a standard error of .13 and P-value of .04.

For comparisons between PA and VG task in the same cohort, agreement in the cortical activations had a Kappa value of .58 and a standard error of .10 with a P-value < .001. For cerebellar activations, the Kappa value was .37 with a standard error of .10 and a P-value < .001. For whether these activations were crossed/uncrossed, the Kappa value was .36 with a standard error of .13 and a P-value of .006. We also used Cohen's Kappa separately on subject groups divided by the hemispheric location of tumors, as shown in Table 1.

Table 1. *Task agreement in subjects with tumors in left or right hemisphere.*

TUMOR HEMISPHERE	TASK	ACTIVATION	KAPPA	STANDARD ERROR	P VALUE
LEFT	VERB GENERATION VS. SEMANTIC ASSOCIATION	Cortical	0.61**	0.12	< 0.001
		Cerebellar	0.06	0.13	0.63
		Crossed/Uncrossed	0.25	0.15	0.088
	VERB GENERATION VS. PHONOLOGICAL ASSOCIATION	Cortical	0.48**	0.12	< 0.001
		Cerebellar	0.38*	0.12	0.001
		Crossed/Uncrossed	0.41*	0.14	0.006
RIGHT	VERB GENERATION VS. SEMANTIC ASSOCIATION	Cortical	1**	0.00	< 0.001
		Cerebellar	-0.03	0.02	0.79
		Crossed/Uncrossed	-0.07	0.05	0.79
	VERB GENERATION VS. PHONOLOGICAL ASSOCIATION	Cortical	0.64*	0.33	0.004
		Cerebellar	-0.05	0.03	0.685
		Crossed/Uncrossed	-0.09	0.07	0.685

Furthermore, the percentage of participants with crossed cerebro-cerebellar activations in the healthy cohort was 78.3% for the VG task, 90.9% for SA and 72.7% for PA. For patients, these percentages were 67.2%, 76.2% and 72.6% respectively. Individual McNemar tests between cortical and cerebellar activations for all the three tasks further validated the presence of significant crossed activations in both groups. For the healthy cohort, the McNemar value was 11.14 with a P-value of .01 for the VG task, 8.77 with a P-value of .03 for the SA task and 11.00 with a P-value of .01 for the PA task. For patients, the McNemar value was 37.36 with a P-value < .001 for VG, 42.87 with a P-value < .001 for SA, and 39.92 with a P-value < .001 for PA.

6.2. Threshold-Independent Lateralization Indices

WF and AveLI values were obtained separately for cortical and cerebellar activations for both cohorts. We tested contralaterality between cerebral and cerebellar activations for each using a Pearson's correlation between the obtained LI values for the cortex and the cerebellum. This was done for all three tasks. The *r* values with their P-values are in Table 2.

From the absolute lateralization values, language activations were then assigned left-, right- or bi-laterality. Activations are classified as left-lateralized for values ranging from 0.1 to 1.0, right-lateralized for values between to –0.1 and –1.0, and symmetric for values between or equal to -0.1 and 0.1 (Suarez et al., 2009; Matsuo et al., 2012).

Table 2. *Pearson's r and their respective P-values for testing contralaterality between the cortical and cerebellar LI values obtained through threshold-independent methods (WLI and AveLI).*

TASK	**PEARSON'S *r***			
	WLI		**AveLI**	
	Controls	**Patients**	**Controls**	**Patients**
Verb Generation	- 0.63** (p = 0.003)	- 0.61** (p < 0.001)	- 0.35 (p = 0.1)	- 0.65** (p < 0.001)
Semantic Association	- 0.53* (p = 0.01)	- 0.14 (p = 0.364)	- 0.58** (p = 0.006)	- 0.19 (p = 0.225)
Phonological Association	- 0.63** (p = 0.002)	- 0.11 (p = 0.493)	- 0.64** (p = 0.001)	- 0.18 (p = 0.242)

Using these values, we also compared language lateralization obtained by the unthresholded method to the laterality assigned by neuroradiologists using a Cohen's kappa test by task for both the cortex and the cerebellum. In the case of WLI in healthy subjects, for the VG task, Kappa value for agreements in cortical activations was .25 with a standard error of .19 and a P-value of .14. For the cerebellum, Kappa was .56 (standard error = .19, P-value = .001). For SA, cortical activations showed high agreement with the Kappa value of .496 (standard error = .17, P-value = .001). As for the cerebellum during SA, the Kappa value was .23 with a standard error of .15 and P-value of .11. For the PA task, the cortical activations showed fair agreement with a Kappa value of .37 with a standard error of .18 and P-value = .03. For the cerebellum, Kappa was .51 (standard error = .15, P-value = .001).

In patients, for the VG task, Kappa value for agreements in cortical activations was .28 with a standard error of .13 and a P-value of .02. For the cerebellum, Kappa was .02 (standard error = .09, P-value = .818). For SA, cortical activations had the Kappa value of -.001 (standard error = .06, P-value = .981). As for the cerebellum during SA, the Kappa value was -.09 with a standard error of .06 and P-value of .087. For the PA task, the cortical activations had a Kappa value of .16 with a standard error of .11 and P-value = .152. For the cerebellum, Kappa was .23 (standard error = .09, P-value = .005).

For AveLI in healthy subjects, the VG task, Kappa value for agreements in cortical activations was .25 with a standard error of .19 and a P-value of .16. For the cerebellum, Kappa was .47 (standard error = .17, P-value = .001). For SA, cortical activations showed high agreement with the Kappa value of .57 (standard error = .16, P-value < .001). As for the cerebellum during SA, the Kappa value was .4 with a standard error of .18 and P-value of .02. For the PA task, the cortical activations showed fair agreement with a Kappa value of .29 with a standard error of .17 and P=value .06. For the cerebellum, Kappa was .21 (standard error = .19, P-value = .18).

In patients, for the VG task, Kappa value for agreements in cortical activations was .47 with a standard error of .13 and a P-value less than .001. For the cerebellum, Kappa was .08 (standard error = .11, P-value = .381). For SA, cortical activations had the Kappa value of .05 (standard error = .06, P-value = .382). As for the cerebellum during SA, the Kappa value was -.07 with a standard error of .07 and P-value of .142. For the PA task, the cortical activations showed fair agreement with a Kappa value of

.31 with a standard error of .12 and P=value .006. For the cerebellum, Kappa was .24 (standard error = .09, P-value = .007).

6.3. Cerebro-Cerebellar White Matter Tracts

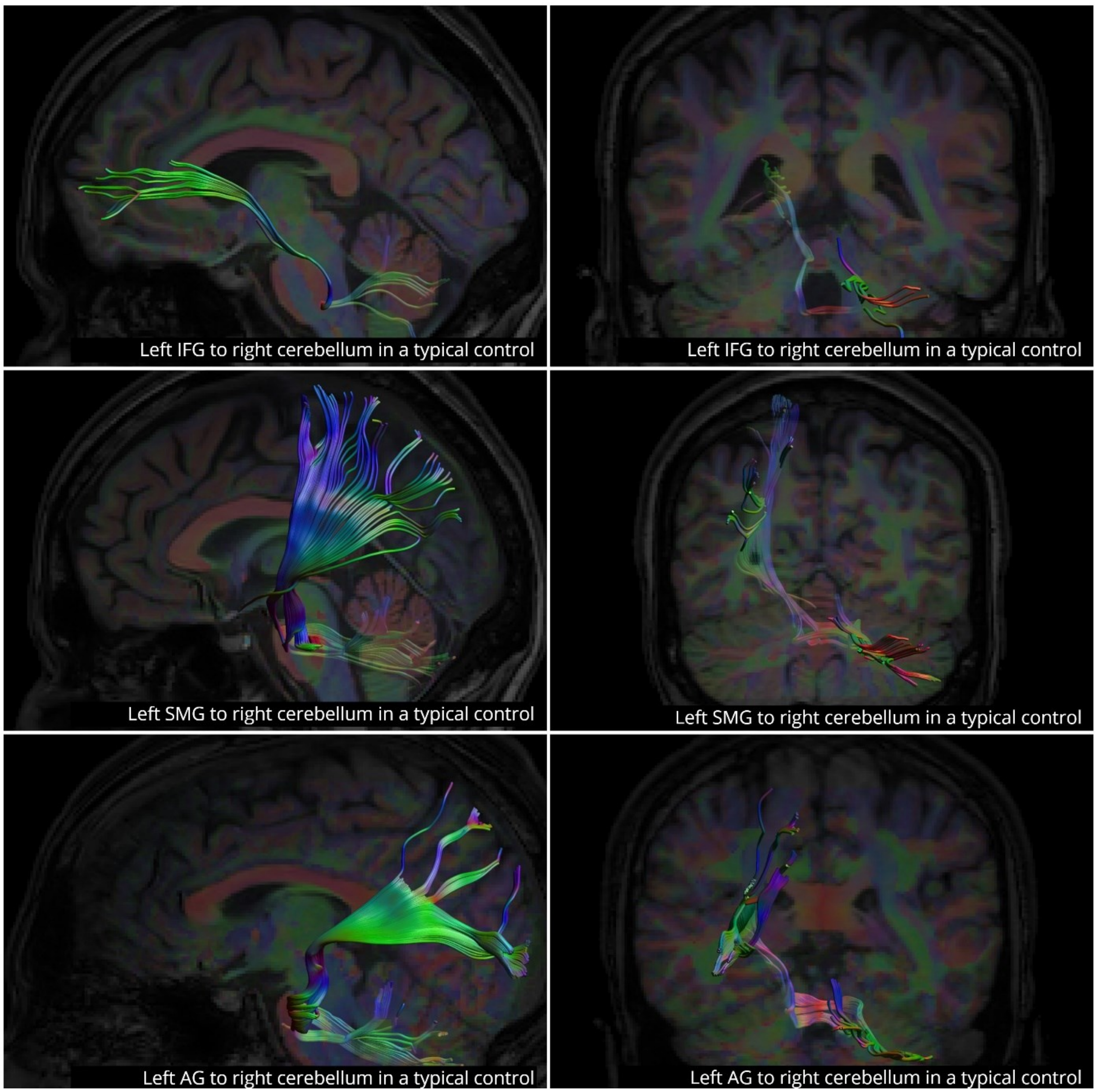

Figure 17. *Representative example of white matter tracts connecting the left IFG, SMG and AG to the right cerebellum in a healthy subject.*

Table 3. *Average FA, MD, angle and length of the white matter tracts observed in healthy subjects and patients. Values are averaged across groups and the numbers in the brackets represent the standard deviation across each group. MD is in mm^2/s, angle in degree and length in mm. LR stands for tracts between the respective left cortical region and right cerebellum and RL is vice versa. Asterisks show LR-RL pairs with a significant difference as obtained in a two-tailed student t-test over means. Additionally, no significant differences were found between the two cohorts.*

		CONTROLS				**PATIENTS**			
		FA	**MD**	**Angle**	**Length**	**FA**	**MD**	**Angle**	**Length**
IFG	**LR**	0.424 (0.016)	0.00082 (0.000058)	6.034 (0.568)	156.994 (39.764)	0.443 (0.046)	0.00083 (0.00010)	5.999 (0.500)	161.876 (33.693)
								*	
	RL	0.425 (0.022)	0.00080 (0.000077)	6.153 (1.108)	184.167 (64.215)	0.440 (0.043)	0.00084 (0.000099)	6.367 (0.652)	176.022 (53.622)
SMG	**LR**	0.473 (0.021)	0.00082 (0.000034)	5.541 (0.180)	186.562 (18.556)	0.467 (0.039)	0.00086 (0.000071)	5.303 (0.462)	188.324 (29.451)
	RL	0.476 (0.034)	0.00082 (0.000050)	5.605 (0.658)	193.035 (26.207)	0.473 (0.056)	0.00085 (0.000097)	5.389 (0.500)	180.250 (34.131)
AG	**LR**	0.454 (0.026)	0.00086 (0.000064)	5.979 (0.399)	223.988 (92.451)	0.439 (0.031)	0.00084 (0.000026)	6.029 (0.639)	201.389 (46.354)
				*			*		
	RL	0.443 (0.032)	0.00087 (0.000067)	5.941 (0.717)	204.305 (36.230)	0.443 (0.029)	0.00091 (0.000072)	5.759 (0.625)	178.662 (26.476)

We identified cortical ROIs in each hemisphere for each subject and analyzed tracts from the contralateral cerebellum to the contralateral ROIs separately. We observed fiber tracts from the left cortex to the contralateral i.e., the right cerebellum in 42.86% of healthy subjects extending to IFG, in 78.57% of the subjects extending to SMG, and in 50% of the subjects extending to AG. 28.57%, 85.71% and 71.43% of total healthy subjects showed the presence of tracts connecting the left cerebellum to the right IFG, SMG and AG respectively. Average FA, mean diffusivity (MD), angle and length for the tracts are shown in Table 3. Figure 17 shows a representative reconstruction of the observed white matter tract between the left IFG, SMG and AG extending to the right cerebellum.

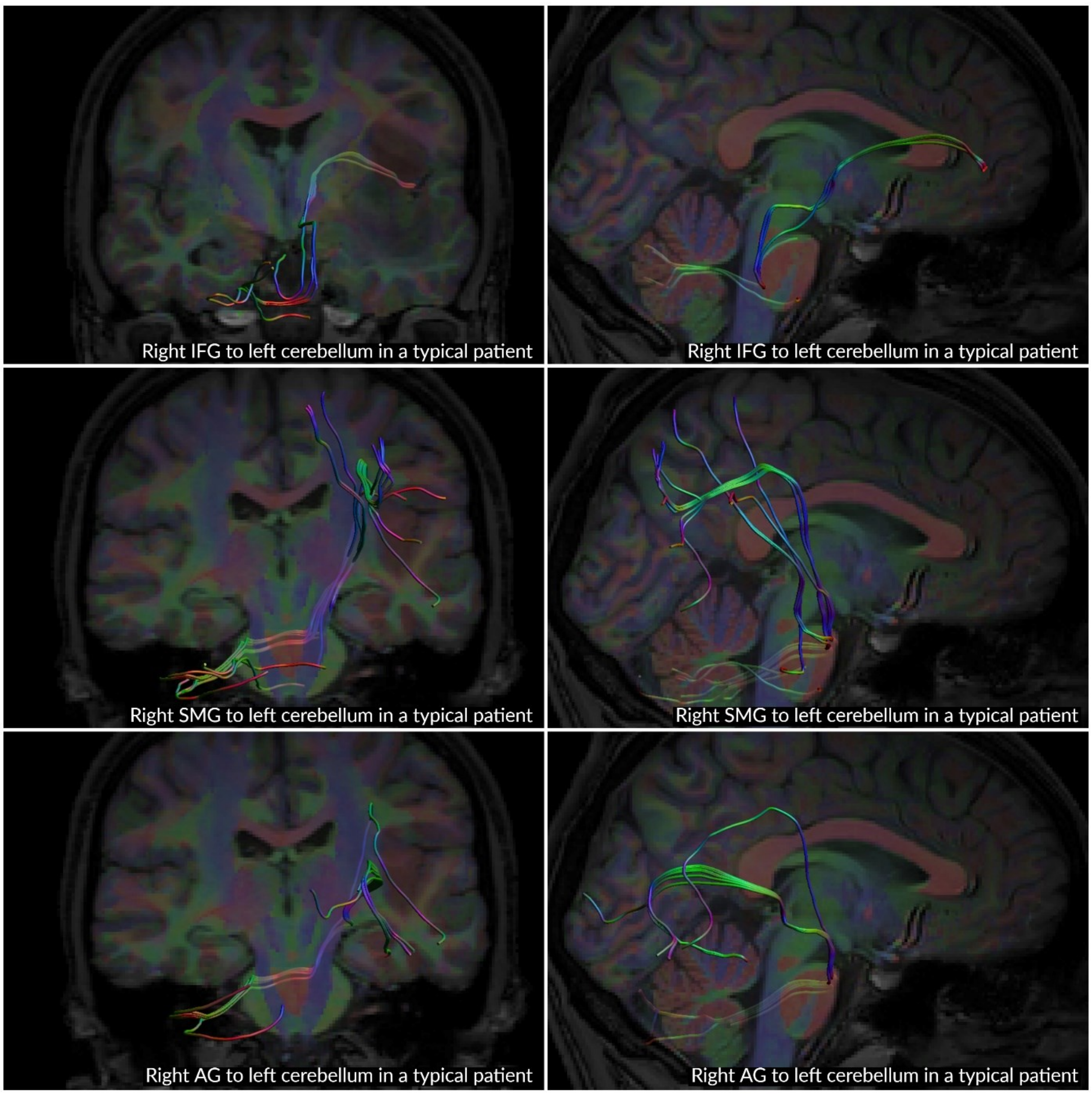

Figure 18. *Representative example of white matter tracts connecting the right IFG, SMG and AG to the left cerebellum in a typical patient.*

For patients, we observed fiber tracts from the left cortex to the contralateral i.e., the right cerebellum in 40.91% of healthy subjects extending to IFG, in 63.64% of the subjects extending to SMG, and in 45.45% of the subjects extending to AG. 31.82%, 68.18% and 40.91% of total healthy subjects showed the presence of tracts connecting the left cerebellum to the right IFG, SMG and AG respectively. Average FA, MD, angle and length for the tracts are shown in Table 3. Figure 18 shows a representative reconstruction of the observed white matter tract between the left IFG, SMG and AG extending to the right cerebellum.

7. DISCUSSION AND CONCLUSIONS

7.1. Crossed Cerebro-Cerebellar Language Activations

In the present work, we demonstrated using Cohen's Kappa, that the SA and PA tasks may be reliable in-clinic paradigms since they both individually show high agreement in lateralization with the traditional VG task in the patient cohort. Cohen's Kappa test checks for agreements between paired categorical variables. The Kappa coefficient value represents the level of agreement where 0-0.2 slight, .2 to .4 fair, .4 to .6 moderate, .6 onwards substantial agreement. Based on this, it can be observed from the results that for healthy subjects, the agreements were only statistically significant for cerebellar activations, and not for cortical activations. This could be due to a smaller *n* for this groups as more than half of the subjects showed activations identical to the verb generation task in the two new tasks. In spite of the lack of agreement observed through the Cohen's kappa test, 73.91% of healthy subjects (17 out of 23 subjects) showed identical lateralization across at least 2 tasks, and 5 subjects showed identical lateralization for all three tasks.

For patients, though, the two tasks have a high and significant agreement with the VG task in lateralization of cortical activation. Fair agreement was also observed for lateralization in cerebellar activation between the VG and PA tasks, and the crossed/uncrossed activation in both comparisons. While no significant agreement was observed between the lateralization of cerebellar activation between the VG and SA tasks, 67.3% of cases had matched lateralization between tasks. Here, 15 out of 18 cases with disagreements between the two tasks were disagreements involving bilateral activation, i.e., only 3 cases had mismatches where they had different one-sided lateralization between tasks. Looking further into task agreement but in the context of hemispheric location of tumors, statistically significant agreements with VG were observed in cortical activations for both tasks and for cerebellar and crossed/uncrossed activations for PA in subjects with tumors in the left hemisphere. Yet, 56% (28 subjects) and 42% (21 subjects) showed agreements in cortical and cerebellar activations for all three tasks respectively for the 50 subjects that had tumors in the left hemisphere. For the 18 subjects with tumors located in the right hemisphere, 94.4% (17 subjects) and 72.2% (13 subjects) showed cortical and cerebellar lateralization agreements respectively. The subject with tumors in both right and left hemispheres showed cerebral lateralization agreement for all tasks and cerebellar agreements in 2 (SA and PA) tasks. It is interesting to note that a higher percentage of subjects with lesions in their right hemisphere showed activation agreements in all three tasks as compared to those with left hemispheric lesions even though the latter had overall better agreements statistically which may warrant further investigation.

A McNemar test further showed significant crossed cerebro-cerebellar activations for all three tasks, establishing the usefulness of these two tasks in language lateralization determination while taking cerebellar activations into account. In the population in general, crossed activations are more prevalent, especially left cortex to right cerebellum. This could be due to the fact that language is mostly left-lateralized (Griggs, 2010), and the right cerebellum is involved by proxy in such cases (Hubrich-Ungureanu et al., 2002). It is also important to note that in healthy subjects, purely ipsilateral cerebellar activations have not been observed. These results not only support our hypothesis but also validate our previous findings extending it to patients with different brain tumor etiology.

As mentioned earlier, VG does not consist of any monitoring modality to confirm subjects are correctly performing it. Tumor presence has been associated with higher level of fatigue in patients (Jakola et al., 2012; Asher et al., 2016) and may also affect language processing itself (Banerjee et al., 2015). These factors may cause patients to underperform this task. Monitoring a patient's performance is especially crucial in a population with an overall lower level of education. Such a patient cohort may have added difficulties in understanding task instructions. Another challenge that commonly presents itself in this context is age. Older adults consistently experience difficulties in word retrieval, which may invoke compensatory mechanisms during task performance (Cabeza, 2002; Wierenga et al., 2008). This phenomenon may result in the engagement of cortical regions not generally involved in language processing, resulting in misleading lateralization evaluation. These particular issues not only highlight the importance of cerebellar activations as a useful feature in lateralization determination, but also the need for paradigms that incorporate overt responses from inside the magnetic resonance scanner.

The SA and PA tasks used in this study incorporated auditory instead of visual stimuli to avoid the difficult conversion of orthographic information to phonological codes and overt articulation (Fiez and Peterson, 1998), and to isolate language processing without additional cognitive demand as observed in older adults (Meinzer et al., 2009). Thus, the tasks used a button-press response from the subjects to semantic and phonological word pairs, respectively. This also helps investigators to keep track of the subject's performance, or lack thereof. It is important to mention here that out of the 69 patients analyzed, only one could not perform the SA task above chance level. The rest had no difficulties or discomfort performing the SA and PA tasks. For 3 (2 for SA and 1 for PA), the scanning needed to be stopped and restarted but only due to technical difficulties. Overall, our cohort revealed better performance for the SA and PA tasks compared to VG.

Moreover, the inclusion of these tasks in presurgical language lateralization may make lateralization determination more robust and well-rounded. VG is a lexical task that recruits the ventral pathway of language processing involving the IFG and the temporal regions (Friederici, 2011). The SA task involves the same regions but has the advantage that it can be monitored. On the other hand, the processing of phonological information as tested by the PA task involves the dorsal pathway that engages parietal regions involved in language processing in addition to the frontal and temporal regions (Friederici, 2017). Especially based on the experience with the current study at our institution, it can be recommended that a paradigm consisting of all these tasks that assess activation for all regions involved in language processing is critical to understand specific language deficits in patients caused by tumor presence. Additionally, the SA and PA tasks are suitable for patients not only with brain tumors, especially the elderly, but also with language disorders in general. These tasks have currently been incorporated actively at our clinic with success. With the results of the study, we urge clinicians to consider the demographic characteristics of their patient population undergoing fMR scanning, including age range and language impairments before designing pre-surgical paradigms. A paradigm consisting of all these tasks that assess activations for all regions involved in language processing is critical to understand specific language deficits in patients of aphasia caused by tumor presence.

With all its merits, the present study also has some limitations. Although overt verbal responses are desirable (Abrahams et al., 2003), this also presents unique challenges for patients with language disorders when trying to limit head motions artifacts during scanning. While the silent gap scanning method may accommodate for this issue (Abrahams et al., 2003), tasks become longer, making the scanning sessions more difficult for a clinical population, especially because it is recommended to incorporate more than one task to correctly identify functional language regions (Zaca et al., 2013). Finally, certain tumor patients may face difficulties in performing tasks that involve auditory cues. Lastly, the study also offers potential for future research. In the present study, these new tasks are used pre-surgically as diagnostic procedures, but they can possibly be used post-surgically to observe whether plasticity due to tumor resection may bring change in language lateralization in patients. It would also be interesting to demonstrate BOLD activation overlap or lack thereof in cerebellar activations for these tasks.

In conclusion, the SA and PA tasks may prove to be useful tools in presurgical crossed cerebro-cerebellar language lateralization determination. This may result in an enhanced prognosis in the clinic, directly benefitting brain tumor patients specifically affected with tumors in eloquent regions.

7.2. Threshold-Independent Lateralization Indices

In the previous subsection, the activations were obtained using methods relying on statistical thresholds that may present nonuniformity in results. As a means to overcome this limitation, this study also evaluates the feasibility of using threshold-independent lateralization methods beyond the bench into the clinic in conjunction with manual expertise. In extension of our previous results in regard to crossed cerebro-cerebellar activations, cortical and cerebellar values obtained for WLI showed a significant negative correlation for all three tasks in healthy subjects. Cortical and cerebellar AveLI values also showed significant negative correlation for the SA and the PA task. Hence, even the threshold-independent LI-based lateralization showed significant crossed cerebro-cerebellar activations in healthy subjects. Meanwhile, significant negative correlation was only observed for the VG task for both LIs in patients.

When compared with manually assigned laterality in the clinic by expert neuroradiologists, the following observations were made. For WLI in healthy subjects, fair to moderate agreement was not observed in activations in the PA task for both cortical and cerebellar activations. High agreements were observed in cerebellar VG activations and cortical SA activations. For patients, significantly fair agreements were observed only in cortical activation during VG and cerebellar activations during PA.

As for AveLI, in healthy subjects, significantly fair to moderate agreement was observed for both cortical and cerebellar lateralization during the SA task. Significant and moderate agreement was also observed in the cerebellar activations for the VG task. For patients, significant moderate agreement was observed for both cortical and cerebellar lateralization during the PA task, and for cortical activations in the VG task.

Based on these results, it can be concluded that threshold-independent LI techniques are not consistently congruent with manually assigned lateralization. It was observed during data analysis that LI values obtained using these techniques have a higher rate of having bilaterality assigned to subjects from both cohorts. This may explain the lack of sufficient agreement with the manually assigned lateralization.

7.3. Cerebro-Cerebellar White Matter Tracts

In terms of the tractography analysis, our results confirm that a good portion of our healthy cohort demonstrated white matter tracts that connect the contralateral cerebellum to the IFG, the SMG and the AG individually. Tracts to the left SMG from the contralateral cerebellum were observed in 78.6% of the subjects, and in 85.71% subjects to the right SMG from the left cerebellum. Occurrence of this tract was observed in 63.64% and 68.18% of patients for each respective side as well. This may point to the cerebellum's involvement in the dorsal stream of language processing. Apart from phonological processing, the dorsal language stream, which SMG is a part of, is also involved in sound localization, speech production and repetition as well as associating lip movements with corresponding sounds (Friederici, 2011). These functions involve a degree of motor control and learning. This would be congruent with current literature that describes the cerebellum's involvement in motor control (Paulin, 1993; Glickstein and Doron, 2008). It is important to note that connections from the right SMG to the left cerebellum were more prevalent than on the other side for both cohorts. The connections to AG also may be explained similarly as AG is also part of the dorsal language pathway. But the connections to AG were only observed relatively less than to SMG. A higher percentage of healthy subjects showed connection from the contralateral cerebellum to the right AG than to the left AG, while the vice versa was the case for patients. Furthermore, the connections to the left IFG were present in more subjects than the right for both cohorts. This, at least, is consistent with literature where specific language functions such as comprehension and production are typically lateralized to the left hemisphere as IFG is part of both the ventral and dorsal language streams (Taylor & Taylor, 1990; Beaumont, 2008). Additionally, this is further supported by visual observation of the obtained tracts which were denser from the left cortex to the right cerebellum than vice versa. But no significant differences between the average FA, MD, angle and lengths of these observed tracts between sides were found. Furthermore, no differences between these factors in tracts in patients and controls were found using an independent samples t-test not assuming equal variance. This may suggest that tumor presence does not affect white matter integrity in patients.

These results warrant further investigation in tractography techniques that may be able to acquire thickness information of the tracts. The discovery of these tracts needs to be followed up with investigation in tractography parameters to consistently construct these pathways that may be sustaining the contribution of the cerebellum in language processing in both healthy and brain tumor cohorts. This is crucial due to the occurrence of false positives and crossing fibers in tractography (Jeurissen et al., 2013). Additionally, a probabilistic tractography approach may assist in the observation of these white matter tracts in a higher number of subjects. In conclusion, the cerebellum’s involvement in the distinct sub-processes of language becomes important in order to explain these differences.

APPENDIX I

Table: *Lesion location and type with other demographic information for participants with brain lesions*

Patient No.	Gender	Age (years)	Histological Assessment	WHO grade classification	Lesion Location	Lesion Hemisphere	Handedness[1]
1	Female	27	Oligodendroglioma	Grade II	Temporal	Right	Right
2	Male	61	Glioblastoma	Grade IV	Middle and Superior Frontal	Right	Right
3	Male	51	Diffuse Astrocytoma	Grade II	Superior Frontal	Right	Right
4	Female	44	Pilocytic Astrocytoma	Grade I	Middle and Inferior Temporal	Right	Right
5	Female	31	Gangliocytoma	Grade I	Inferior Temporal	Left	Right
6	Female	38	Oligodendroglioma	Grade II	Parieto-occipital	Left	Right
7	Female	60	Glioblastoma	Grade IV	Middle and Inferior Frontal	Right	Right
8	Female	31	Diffuse Astrocytoma	Grade II	Parietal	Left	Right
9	Male	22	Diffuse Astrocytoma	Grade II	Frontotemporal	Right	Right
10	Male	76	Glioblastoma	Grade IV	Middle Temporal	Left	Right
11	Male	65	Glioblastoma	Grade IV	Inferior Frontal	Left	Right
12	Male	25	Diffuse Astrocytoma	Grade II	Inferior Parietal	Left	Right
13	Male	31	Diffuse Astrocytoma	Grade II	Frontoparietal Insular	Right	Right
14	Male	48	Oligodendroglioma	Grade II	Middle Frontal	Left	Right
15	Male	58	Metastasis	N/A	Occipitoparietal	Left	Right
16	Female	42	Diffuse Astrocytoma	Grade II	Superior Frontal	Left	Right
17	Female	33	Diffuse Astrocytoma	Grade II	Inferior Frontal	Left	Right
18	Female	55	Anaplastic Astrocytoma	Grade III	Frontoparietal	Left	Right
19	Male	78	Primary CNS lymphoma	N/A	Parietal	Left	Right

20	Female	38	Oligodendroglioma	Grade II	Inferior Frontal	Left	Left
21	Female	55	Primary CNS lymphoma	N/A	Parietal	Left	Right
22	Male	65	Glioblastoma	Grade IV	Temporal	Left	Right
23	Female	34	Inconclusive primary tumor	N/A	Superior Frontal	Left	Right
24	Female	57	Metastasis	N/A	Parietal	Right	Right
25	Female	43	Anaplastic Astrocytoma	Grade III	Frontotemporal	Left	Right
26	Male	64	Glioblastoma	Grade IV	Middle Frontal	Left	Right
27	Male	52	Glioblastoma	Grade IV	Temporal	Left	Right
28	Female	31	Anaplastic Oligodendroglioma	Grade III	Frontotemporal	Left	Right
29	Female	39	Anaplastic Ependymoma	Grade III	Temporal Insular	Left	Right
30	Female	61	Glioblastoma	Grade IV	Occipital	Left	Right
31	Female	37	Diffuse Astrocytoma	Grade II	Frontotemporal	Left	Right
32	Female	40	Oligodendroglioma	Grade II	Superior Frontal	Left	Right
33	Male	29	Anaplastic Astrocytoma	Grade III	Middle Temporal	Left	Right
34	Female	70	Glioblastoma	Grade IV	Frontotemporal	Right	Right
35	Male	20	Primary Infectious Tuberculoma	N/A	Frontoparietal	Left	Right
36	Female	36	Diffuse Astrocytoma	Grade II	Superior Frontal	Right	Right
37	Female	30	Anaplastic Astrocytoma	Grade III	Temporal	Left	Right
38	Male	57	Metastasis	N/A	Middle Temporal	Left	Right
39	Female	30	Primary Cortical Dysplasia	N/A	Superior Frontal	Left	Right
40	Male	32	Anaplastic Oligodendroglioma	Grade III	Frontotemporal	Right	Right
41	Female	53	Metastasis	N/A	Frontoparietal	Left	Right

42	Female	67	Oligodendroglioma	Grade II	Frontoparietal	Right	Right
43	Female	53	Anaplastic Oligodendroglioma	Grade III	Frontal	Right	Right
44	Male	26	Oligodendroglioma	Grade II	Frontal	Right	Right
45	Female	30	Anaplastic Oligodendroglioma	Grade III	Occipital	Left	Left
46	Female	33	Glioblastoma	Grade IV	Frontal	Left	Right
47	Male	41	Inconclusive primary tumor	Not yet operated	Temporal	Left	Right
48	Male	40	Anaplastic Astrocytoma	Grade III	Frontal	Left	Right
49	Male	29	Anaplastic Oligodendroglioma	Grade III	Temporal	Left	Right
50[2]	Female	52	Oligodendroglioma	Grade II	Temporal	Left	Right
51	Male	22	Inconclusive primary tumor	Not yet operated	Precentral	Right	Right
52	Male	56	Anaplastic Oligodendroglioma	Grade III	Temporal	Left	Right
53	Female	64	Glioblastoma	Grade IV	Temporal	Right	Left
54	Female	60	Oligodendroglioma	Grade II	Frontal	Left	Right
55	Male	28	Diffuse Astrocytoma	Grade II	Temporal	Right	Right
56	Male	48	Glioblastoma	Grade IV	Temporal	Left	Right
57	Female	58	Glioblastoma	Grade IV	Temporoparietal	Left	Right
58	Female	37	Metástasis	N/A	Temporal	Left	Right
59	Female	65	Metastasis	N/A	Left Frontal, Right Temporal	Bilateral	Right
60	Male	53	Diffuse Astrocytoma	Grade II	Temporal	Left	Right
61	Male	29	Diffuse Astrocytoma	Grade II	Frontotemporal	Left	Right

62	Female	53	Glioblastoma	Grade IV	Temporal	Left	Right
63	Female	32	Glioblastoma	Grade IV	Occipito-temporal	Left	Right
64	Male	45	Diffuse Astrocytoma	Grade II	Temporal	Left	Right
65	Male	49	Metastasis	N/A	Frontal	Left	Right
66[2]	Male	54	Glioblastoma	Grade IV	Temporal	Left	Right
67	Female	40	Anaplastic Astrocytoma	Grade III	Frontotemporal Insular	Left	Right
68	Female	66	Inconclusive primary tumor	Not yet operated	Frontal	Left	Right
69	Male	24	Oligodendroglioma	Grade II	Occipital	Right	Right
70	Male	75	Glioblastoma	Grade IV	Parietal	Left	Right
71	Male	19	Diffuse Astrocytoma	Grade II	Subcentral Frontal	Left	Right

WHO: World Health Organization
N/A: not applicable
[1]: measured with Edinburgh Handedness Test
[2]: Excluded from Analysis

APPENDIX II

A selection of behavioral tests

TEST DE VOCABULARIO DE BOSTON FORMATO ABREVIADO

Ítem	Respuesta	Respuesta correcta	Latencia (segundos)	Clave semántica	Clave fonética	Código(s) de error	Elección múltiple
1.	casa . . . . (un tipo de edificio)	______	______	______	______	______	______
2.	peine . . . . (sirve para arreglarse el cabello)	______	______	______	______	______	______
3.	cepillo de dientes . . . (se usa en la boca)	______	______	______	______	______	______
4.	pulpo . . . . (un animal marino)	______	______	______	______	______	______
5.	banco . . . . (sirve para sentarse)	______	______	______	______	______	______
6.	volcán . . . . (un tipo de montaña)	______	______	______	______	______	______
7.	canoa . . . . (se usa en el agua)	______	______	______	______	______	______
8.	castor . . . . (un animal)	______	______	______	______	______	______
9.	cactus . . . . (algo que crece)	______	______	______	______	______	______
10.	hamaca . . . . (sirve para descansar)	______	______	______	______	______	______
11.	fonendoscopio . . . . . (lo usan los médicos)	______	______	______	______	______	______
12.	unicornio . . . . (animal mítico)	______	______	______	______	______	______
13.	trípode . . . . (lo usan los fotógrafos)	______	______	______	______	______	______
14.	esfinge . . . . (se encuentra en Egipto)	______	______	______	______	______	______
15.	paleta . . . . (la usan los artistas)	______	______	______	______	______	______

CÓDIGO DE ERRORES

Los siguientes códigos de errores se utilizan para categorizar las respuestas incorrectas. El código de error debe ser anotado en la columna designada para ello.

pf	Parafasia fonémica con resultado de no-palabra
pf/v	Parafasia fonémica con resultado de palabra (Se puntúa como parafasia fonémica cuando se conserva más del 50% de la fonología de la palabra-objetivo).
v	Parafasia verbal, relacionada semánticamente con la palabra-objetivo
v/nr	Parafasia verbal no relacionada con la palabra-objetivo
n	Neologismo (menos de 50% de superposición con la fonología de la palabra-objetivo)
mp	Parafasia de múltiples palabras/error paragramático
ea	Otras emisiones o comentarios ajenos al objetivo (no considerados parafasia)
cl	Circunloquio (no considerado parafasia)
p	Perseveración
per	Error perceptivo

TOKEN TEST (De Renzi, 1978)

Repetición (sólo 1 vez) tras respuesta incorrecta y tras no reacción dentro de 5 segundos
Parar la evaluación tras 5 errores consecutivos

1 = Respuesta correcta o después de auto-corrección
½ = Respuesta correcta tras repetición
0 = Respuesta Incorrecta

Posicionar hoja con los círculos grandes al lado del participante

"Usted ve aquí cuadrados y círculos (indicar). *Algunos son grandes y otros son chicos* (indicar). *Hay de color rojo, negro, verde amarillo y blanco (tocar cada uno). Le pediré que toque algunos de ellos"*
En caso que el participante pregunte "¿Cuál?", responder: *"El que usted quiera, toque cualquier círculo"*

Tocar 1: Hoja con todas las figuras	**1 ½ 0**
1. Toque un círculo	
2. Toque un cuadrado	
3. Toque el color amarillo	
4. Toque el color rojo	
5. Toque el color negro	
6. Toque el color verde	
7. Toque el color blanco	

Tocar 2: Hoja con figuras grandes	**1 ½ 0**
1. Toque el cuadrado amarillo	
2. Toque el círculo negro	
3. Toque el círculo verde	
4. Toque el cuadrado blanco	

Tocar 3: Hoja con todas las figuras	**1 ½ 0**
1. Toque el círculo blanco chico	
2. Toque el cuadrado amarillo grande	
3. Toque el cuadrado verde grande	
4. Toque el círculo negro chico	

TOKEN TEST (De Renzi, 1978)

Repetición (sólo 1 vez) tras respuesta incorrecta y tras no reacción dentro de 5 segundos
Parar la evaluación tras 5 errores consecutivos

"Le pediré ahora tocar 2 figuras. Usted debe comenzar una vez que haya terminado de darle la instrucción"

Tocar 4: Hoja con figuras grandes	**1 ½ 0**
1. Toque el círculo rojo y luego el cuadrado verde	
2. Toque cuadrado amarillo y luego el cuadrado negro	
3. Toque el cuadrado blanco y luego el círculo verde	
4. Toque el círculo blanco y luego el círculo rojo	

Tocar 5: Hoja con todas las figuras	**1 ½ 0**
1. Toque el círculo blanco grande y el cuadrado verde chico	
2. Toque el círculo negro chico y el cuadrado amarillo grande	
3. Toque el cuadrado verde grande y el cuadrado rojo grande	
4. Toque el cuadrado blanco grande y el círculo verde chico	

Disponer fichas según la hoja con figuras grandes (círculos al lado del paciente).

"Le pediré ahora seguir instrucciones con las figuras."

NO repetir las instrucciones

Reeks 6: grande tokens	**1 0**
1. Deje el círculo rojo encima el cuadrado verde	
2. Toque el círculo negro con el cuadrado rojo	
3. Toque de círculo negro y el cuadrado rojo	
4. Toque el círculo negro o el cuadrado rojo	
5. Deje el cuadrado verde lejos del cuadrado amarillo	
6. Si hay un círculo azul, toque el cuadrado rojo	
7. Deje el cuadrado verde al lado del círculo rojo	
8. Toque los cuadrados lentamente y luego los círculos rápidamente	
9. Deje el círculo rojo entre el cuadrado amarillo y el cuadrado verde	
10. Toque todos los círculos menos el verde	
11. Toque el círculo rojo ¡No perdón! el cuadrado blanco	
12. En vez de tocar el cuadrado blanco, toque el círculo amarillo	
13. Además del círculo amarillo, toque el círculo negro	

Total: ____________

Puntaje < 29 = afásico

APPENDIX III

Journal Publications

Thakkar I, Arraño-Carrasco L, Cortes-Rivera B, *et al.* Alternative language paradigms for functional magnetic resonance imaging as presurgical tools for inducing crossed cerebro-cerebellar language activations in brain tumor patients. ***European Radiology.*** **2021**. https://doi.org/10.1007/s00330-021-08137-9

Thakkar I, Massardo T, Pereira J, *et al.* Identification of Statin's Action in a Small Cohort of Patients with Major Depression. ***Applied Sciences*****. 2021**. https://doi.org/10.3390/app11062827

Conference Oral Presentations

Thakkar I, Arraño-Carrasco L, Cortés-Rivera B, Zunino-Pesce R, Mendez-Orellana CP. Cortical Bilaterality and Cerebellar Involvement in Semantic and Phonological Processing with Age. **International Online Workshop on Language in Healthy and Pathological Aging (AGELANG), 2021**, Online.

Thakkar I. Language Processing and The Role of Cerebellum in Brain Tumor Patients. Workshop 5: Medicine and Biology, Alexander von Humboldt Foundation's virtual event **Early Career Researchers WANTED! Chile's next Generation of Humboldtians, 2021**, Online.

Most Recent Conference Poster Proceedings

Thakkar I, Arraño-Carrasco L, Zunino-Pesce R, Cortés-Rivera B, Mery-Muñoz F, Rodriguez-Fernandez M, Leemans A, Mendez-Orellana CP. *Investigating the Cerebellar Connectivity of Language Processing: A DTI Feasibility Study.* **Society for Neuroscience 50th Annual Meeting 2021**, Online.

Thakkar I, Arraño-Carrasco L, Cortés-Rivera B, Zunino-Pesce R, Mery-Muñoz F, Smits M, Mendez-Orellana CP. *BOLD activations in the cerebellum as an additional diagnostic feature for determination of language lateralization.* **Society for Neuroscience Global Connectome 2021**, Online.

Thakkar I, Arraño-Carrasco L, Cortés-Rivera B, Zunino-Pesce R, Mery-Muñoz F, Smits M, Mendez-Orellana CP. *Alternative Presurgical fMRI Language Paradigms for Inducing Crossed Cerebro-Cerebellar Language Activations in Brain Tumor Patients.* **XVI Reunión Anual de la Sociedad Chilena de Neurociencia 2020**, Online.

Thakkar I, Rana M, Salinas C, Silva C, Brett C, Pereira J, Sitaram R, Ruiz S. *A Real-time fMRI-based Neurofeedback System for Rehabilitation of Depressive Symptoms*. **10th International Brain Research Organization World Congress of Neuroscience 2019**, Daegu, Republic of Korea.

Thakkar I, Rana M, Salinas C, Silva C, Brett C, Pereira J, Sitaram R, Ruiz S. *Effect of Multi-ROI rtfMRI-based Brain-Regulation on Mood in Depression.* **Organization of Human Brain Mapping Annual Meeting 2019**, Rome, Italy.

Thakkar I, Rana M, Torres R, Ruiz S, Sitaram R. *Effect of Contingent Reward on Learning Self-Regulation in the SMA using fNIRS-Based Neurofeedback.* **Organization for Human-Brain Mapping Annual Meeting 2018**, Singapore.

Thakkar I, Lagos W, Rana M, Sulzer J, Torres R, Ruiz S, Sitaram R. *The Effect of Reward on Brain Self-Regulation Acquired through fNIRS Neurofeedback.* **Real-time Functional Imaging and Neurofeedback Conference 2017**, Nara, Japan.

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