Brain structural predispositions for music and language processing

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"Heart is the engine of your body,

but Brain is the engine of your life"

Michael Cretu *(Enigma)*

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This work and the amazing trip that has made it possible, are unbelievably (and somehow surrounded by a magical atmosphere) arriving to its end. And due to that nostalgia that attacks us at the end of the chapter in a well-written book, in the first moments right after the words ‘The End’ have danced on the screen, in the static second after the last bar of a musical piece has been played in a concert and one can still smell the scent of that last chord, I cannot help thinking in all those ‘coincidences’ that have brought me exactly to this point. Reading about Ramon y Cajal’s hypothesis about brain plasticity when I was just a child, completing my secondary education in a high-school with Cajal’s name, some of my physiotherapy teachers showing me a world full of possibilities and gaps to fill in research, my passion for music driving me from wanting to play to wanting to understand musicians’ bodies and music learning, moving from one city to another, crossing paths with people that was already determined to complete a PhD… As Boris Cyrulnik said, “The paradox of the human condition, is that you can become yourself just under the influence of others”. Thus, as a trip in which I have learnt and grown so much, both personal and professionally, and before closing this important chapter in my life, I must try to put in words how thankful I am for the wonderful people I have in my life that have supported me through the space and time, and that have helped me in completing this great journey. I could not have done any of this without a lot of people that have been by my side, that have contributed in a more or less direct way to this work, in a scientific and/or personal way. So, in no particular order (or language, for that matter) I would like to thank and dedicate this thesis to the following people.

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por mantener la cordura y hacer

que hasta el peor de los días valga la pena.

Abstract

It has been shown that music and language training can elicit plastic changes on brain structure and function bringing along behavioural benefits. For instance, musicians have been reported to have better auditory discrimination including pitch and speech-in-noise perception, motor-synchronization, verbal memory and general IQ than individuals without formal musical background. Also, bilinguals have shown higher executive function and attention-related abilities than monolinguals. Furthermore, altered functional and structural connectivity can be tracked to brain areas related to the activities most frequently performed by both musicians (instrumentalists and singers) and linguistic experts (such as bilinguals or professional phoneticians).

While research in the last decade has devoted important effort to the study of brain plasticity, only a few investigations have addressed the connection between the initial functional or structural properties of brain networks related to auditory-motor function and subsequent language or musical training. Indeed, brain structural markers such as grey matter volume/density or white-matter diffusivity measurements from diffusion tensor imaging (DTI) data, as well as functional measurements from task-related activity or resting-state data from magnetic resonance imaging (MRI) or electroenceplhalography (EEG) have been demonstrated to correlate with consecutive performance and learning in the auditory-motor domain.

The main goal of the present dissertation was twofold: we aimed to further the existing knowledge regarding brain plasticity elicited during putative sensitive periods and after long-term music practice, and to explore the white-matter pathways that predict linguistic or musical skills at baseline . Our secondary goals were to confirm previous findings regarding the brain structures involved in music and language processing, as well as to provide evidence of the benefits of usingstructural measurements and correlational analyses between imaging and behavioural data to study inter-individual differences.

Study I focused on the comparison between professional pianists and non-musicians observing a complex pattern of increases and decreases in grey matter volume. In comparison to non-musician individuals, pianists showed greater grey matter volume in areas related to motor skill and the automatization of learned movements, as well as reinforcement learning and emotional processing. On the other hand, regions associated to sensorimotor control, score reading and auditory and musical perception presented a reduction in grey matter volume.

Study II explored the relationship between white-matter structural properties of the arcuate fasciculus (AF) and the performance of native German speakers in a foreign-language (Hindi) sentence and word imitation task. We found that a greater left lateralization of the AF volume predicted performance on the imitation task. This result was confirmed by using not only a manual deterministic approach but also an automatic atlas-based fibre-reconstruction method, which in addition pointed out to a specific region in the anterior half of the left AF as the most related to imitation ability.

Study III aimed to investigate whether the white-matter structural connectivity of the pathways previously described as targets for plasticity mechanisms in professional musicians predicted musical abilities in non-musicians. We observed that the white-matter microstructural organization of the right hemisphere pathways involved in motor-control (corticospinal tract) and auditory-motor transformations (AF) correlated with the performance of non-musician individuals during the initial stages of rhythmic and melodic learning.

The present work confirmed the involvement of several brain structures previously described to display plastic effects associated to music and language training in the first stages of audio-motor learning. Furthermore, they challenge previous views regarding music-induced plasticity by showing that expertise is not always or uniquely correlated with increases in brain tissue. This raises the question of the role of efficiency mechanisms derived from professional-like practice.

Most importantly, the results from these three studies converge in showing that a prediction-feedback-feedforward loop for auditory-motor processing may be crucially involved in both musical and language learning and skills. We thus suggest that brain auditory-motor systems previously described as participating in native language processing (cortical areas of the dorsal route for language processing and the AF that connects them) may also be recruited during exposure to new linguistic or musical material, being refined after sustained music practice.

Resumen

Estudios previos muestran que la formación musical y lingüística provoca cambios plásticos en las estructuras y funciones cerebrales, acompañándose también de beneficios conductuales. Por ejemplo, se ha descrito que los músicos poseen mejores habilidades de discriminación auditiva (incluyendo la percepción tonal y la discriminación del habla en un ambiente ruidoso), una mayor capacidad de sincronización motora, así como mejor memoria verbal y coeficiente intelectual general en comparación con personas sin formación musical. Paralelamente, los bilingües muestran mejores funciones ejecutivas y habilidades relacionadas con la atención en comparación con individuos monolingües. Además, las alteraciones en la conectividad cerebral funcional y estructural pueden ser rastreadas estudiando las áreas cerebrales relacionadas con las actividades más utilizadas por músicos (instrumentistas y cantantes) y expertos lingüísticos (como bilingües o fonetistas profesionales).

Pese a que en la última década se han dedicado esfuerzos importantes en el campo de la investigación sobre la plasticidad cerebral, sólo unos pocos estudios han tratado de investigar la conexión entre las propiedades iniciales del cerebro, en cuanto a las funciones y estructuras que se relacionan con las funciones auditivo-motoras, y el posterior aprendizaje musical o del lenguaje. Sin embargo, los marcadores estructurales cerebrales, tales como volumen/densidad de materia gris o medidas de difusividad en la sustancia blanca a partir de datos de imagen del tensor de difusión, así como medidas funcionales de la actividad relacionada con una tarea o datos de *resting-state* (estado de reposo) obtenidos por resonancia magnética o electroencefalografía, han demostrado que pueden correlacionar con el rendimiento y el aprendizaje en el dominio auditivo-motor.

En la presente tesis pretendíamos ampliar nuestro conocimiento en cuanto a la plasticidad cerebral obtenida durante los supuestos “períodos sensibles” y después de la práctica musical mantenida en el tiempo, por un lado, y explorar las vías de sustancia blanca que pueden predecir habilidades lingüísticas o musicales al inicio del aprendizaje, por otro lado. Como objetivos secundarios, queríamos confirmar resultados previos con respecto a las estructuras cerebrales involucradas en el procesamiento de la música y el lenguaje, así como apoyar el uso de mediciones estructurales y enfoques correlacionales (entre datos de neuroimagen y conductuales) para estudiar las diferencias inter-individuales.

El Estudio I se centró en la comparación entre pianistas profesionales y no músicos, observando un complejo patrón de aumentos y disminuciones en el volumen de materia

gris. En comparación con los individuos no músicos, los pianistas mostraron mayor volumen de sustancia gris en áreas relacionadas con la habilidad motora y la automatización de movimientos aprendidos, así como el aprendizaje a través del refuerzo y el procesamiento emocional, mientras que las regiones asociadas al control sensoriomotor, lectura de partituras y percepción auditiva y musical presentaron una reducción del volumen de materia gris.

El Estudio II exploró la relación entre las propiedades estructurales de la materia blanca del fascículo arqueado (AF por sus siglas en inglés) y el rendimiento de hablantes nativos de alemán en una tarea de imitación de frases y palabras en una lengua extranjera (hindi). Encontramos que una mayor lateralización del volumen de AF hacia la izquierda predecía el desempeño en la tarea de imitación. Este resultado se confirmó utilizando no sólo un enfoque determinístico-manual sino también una reconstrucción automática (basada en atlas anatómicos) de las fibras de sustancia blanca que, además, señalaba una región específica en la mitad anterior del AF izquierdo como la más relacionada con las capacidades de imitación.

El Estudio III tenía como objetivo investigar si la conectividad estructural de vías de sustancia blanca anteriormente descritas como dianas para los mecanismos de plasticidad en músicos profesionales, podría predecir las habilidades musicales en los no músicos. Se observó que la organización micro-estructural de la materia blanca en el hemisferio derecho en vías involucradas en el control motor (tracto corticoespinal) y en transformaciones auditivo-motoras (AF) correlacionaba con el desempeño de individuos no músicos en las etapas iniciales del aprendizaje rítmico y melódico.

El presente trabajo ha confirmado la implicación en las primeras etapas del aprendizaje audio-motor de varias estructuras cerebrales que previamente habían mostrado efectos plásticos asociados al aprendizaje musical y del lenguaje. Además, estos resultados desafían las opiniones anteriores sobre la plasticidad inducida por la experiencia musical al demostrar que la experiencia no se correlaciona siempre ni únicamente con un aumento del tejido cerebral, y planteando así preguntas sobre los mecanismos de eficiencia derivados de la práctica musical a nivel profesional.

Más importante aún es que los resultados de estos tres estudios convergen mostrando que un bucle de predicción–retroalimentación (feedback)–alimentación directa (feedforward) para el procesamiento auditivo-motor puede estar implicado de manera crucial tanto en el aprendizaje musical como en el aprendizaje de idiomas. Por tanto, sugerimos que los sistemas auditivo-motrices del cerebro, que previamente se habían descrito como participantes en el procesamiento del lenguaje nativo (áreas corticales involucradas en la vía dorsal para el procesamiento del lenguaje, y el AF, que las conecta) también pueden ser reclutados durante la exposición a material lingüístico o musical nuevo, siendo refinado tras años de práctica musical activa.

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Preface

We are all familiar with the classical concept that every single individual is a product of the interaction between genetic factors and environmental experiences. We all receive a pack of genes from our parents containing information that has been transmitted generation after generation in our families. This genetical information determine all our physical characteristics (phenotype), which in turn would affect how we act, how well prepared would we be for behavioural success, or which risks of developing specific diseases would we have.

Research in the last century has provided us with large and important evidence about neuroplasticity, about how malleable are our brains depending on the specific requirements of the environment. Moreover, epigenetical processes have been described as well, opening a whole world of possibilities about the determinants of human behaviour. Taking this into account, it is not only our direct experience that matters and is able to alter our brain structure and function; the experiences lived by our parents can have an effect on how the genetic material is expressed, with molecular/cellular mechanisms that mediate and record the consequences of those experiences, transmitting this information to following generations.

This genetical and epigenetical background predisposes us to experience the world in a certain manner and, as some researchers have proposed, it may predispose us to seek out for the environment and activities that fulfill our innate skills. Furthermore, the reactions obtained by the environment to our actions, behavioural performance and talents, may also influence the course of our normal development as well as the context we will choose.

Learning, practice and experience have demonstrated to possess a measurable effect in brain structure and function, altering both the anatomy and the way in which the brain processes information (related to the learned domain or to different domains). But the baseline state of our brains before the training starts is as crucial as the neuroplastic changes directly elicited by the learning or experience. The sequence of events that ends with a system possesing some factors that could act as an advantatge for learning a new language or success in music playing, for example, or the causes of these advantatgeous or discouraging predispositions towards different experiences, are still unknown. Moreover, the possibilities of interactions between neuroplastic phenomena and genetic and epigenetic predispositions and changes remain both broad and unclear.

At systems level, magnetic resonance imaging methods have proven to be useful in the study of predispositions and neuroplasticity effects. However, these techniques possess important limitations, and more research is still needed in order to corroborate previous and present findings, as well as to obtain a clear link between imaging measures and cellular/molecular processes.

This dissertation contains three original experiments in the framework of cognitive neurosciences, aiming to explore the neural substrates underlying musical and linguistic predispositions as well as neuroplastic effects of long-term music practice. The present thesis is thus cetred in studying individual differences related to musical and linguistic skills, as well as comparing the brain anatomy of musicians and non-musicians, with a special interest in the effect of age of start of musical training among the musicians group. The thesis is organized in the following way:

Chapter 1: contains an overview of the previous research in the field, explaining the framework in which the experiments performed in this work are contained.

Chapter 2: describes the general goal of this dissertation as well as the aims of the three experiments of the thesis.

Chapter 3: contains the first experiment, in which we obtained structural neuroimaging data from a group of professional pianists and a cohort of non-musicians, in order to study anatomical regions in which the groups may differ. Moreover, the pianists also completed a scale-playing task in the piano and a questionnaire regarding their hours of current and past practice and the age of start of musical practice, allowing us to study the effects of age of acquisition of piano training, ruling out the effect of hours of practice. In comparison with non-musicians, pianists showed increased grey matter volume in a network involved in reinforcement learning, and decreased grey matter volume in regions related to sensorimotor control, auditory processing and score-reading. Furthermore, early-trained pianists outperformed late-trained piansits in the scale-playing task (they showed better temporal precission), and showed less volume of grey matter in the right putamen. Results from this experiment have been published in *NeuroImage* journal.

Chapter 4: includes the second experiment, in which a native-German-speakers cochort completed an imitation task of a language to which they have never been exposed before (i.e., Hindi). Subjects were asked to imitate sentences and a word after listening only 3 times to each stimulus, without any further exposure or rehaearsal. Imitation performance was recorded, rated by native Hindi speakers, and then correlated with diffusion-weighted images. Concretely, imitation scores were correlated with diffusivity and volumetrical values extracted from the arcuate fasciculus (which was virtually dissected using two techniques: a manual and an automatic one). We found that a larger lateralization of the volume of the arcuate fasciculus toward the ñeft hemisphere predicted the performance of our participants in the Hindi imitation task. These results have been recently published in *Cerebral Cortex*.

Chapter 5: contains the third and final experiment in which a cohort of non-musicians completed a single session of musical training, always after a scan session in which diffusion-weigthed data was obtained. We reconstructed the corticospinal tract and the arcuate fasculus via manual deterministic dissections and correlated the diffusivity and volumetrical properties of these tracts with performance scores in a rhythm synchronization task and a melody-learning (piano) task. The corticospinal tract seems to show a specialization for rhythmic skills, while the arcuate fasciculus appears to act in a domain-general way, underlying the learning of both rhytm and melodic sequences.

Chapter 6: discloses the general discussion, contextualizing the results from the three experiments, and commenting some limitations, future directions and the importance and novelty they offer to the field.

Chapter 7: contains the general conclusion and final remarks.

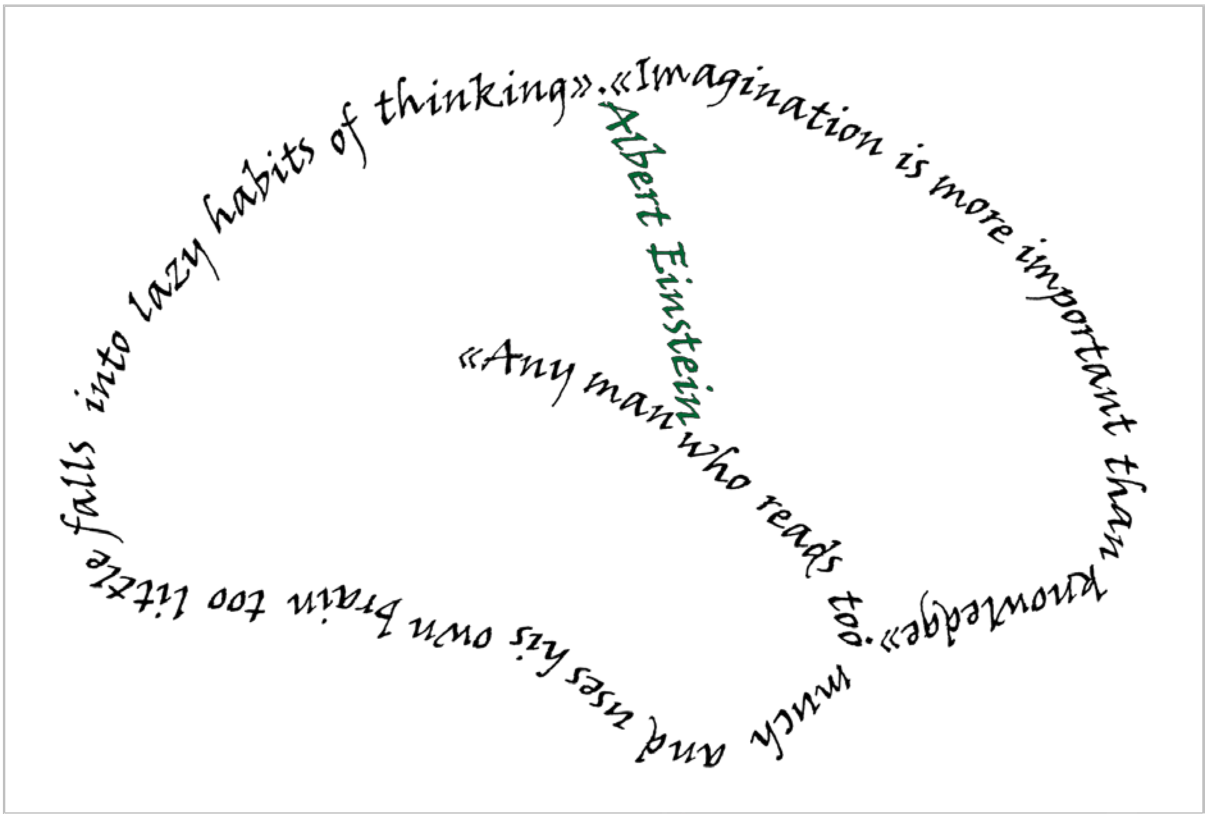
Chapter 8: holds a brief summary of the introduction, objectives, results and discussion of the dissertation in Spanish language.

Chapter 9: includes the bibliographic references cited outside the experimental chapters (i.e., the introduction, general discussion and conclusion).

Frequently used abbreviations

AF	Arcuate fasciculus
CST	Corticospinal tract
DTI	Diffusion Tensor Imaging
GM	Grey matter
HS	Heschl's gyrus
IFG	Inferior Frontal Gyrus
MRI	Magnetic Ressonance Imaging
PMC	Premotor cortex
SMA	Supplementary Motor Area
STG	Superior Temporal Gyrus
TBSS	Tract-Based Spatial Statistics
VBM	Voxel-Based Morphometry
WM	White matter

Chapter 1 - Introduction



1.1 Da capo (remembrance of the beginning)

Music has been always a central part of my life and my everyday routines since as far as I can remember. I have been always fascinated by the potential that music possesses to empower us, to change our feelings, to make us share emotions with others… Being part of a 'musical' family and having received musical education from childhood, several times throughout my lifetime I found myself thinking about all the benefits that music have brought to my life, how I have the feeling that the discipline that I learned in my cello lessons have helped me to be more organized for studying the different lectures in school and high-school, or that I was a little bit more advantaged for learning new languages due to the fact that I practiced my auditory discrimination on a daily basis thanks to my music lessons or my cello-practice.

When I started this PhD journey and arrived to the Cognition and Brain Plasticity research group, I discovered that some of my thoughts regarding music cognition, music-derived benefits and transfer of music abilities to other domains, have been questioned and tested several times by great researchers around the world, and that at this very same lab, some of my partners were also willing to increase our knowledge about those music-related questions. I soon learned that this field of research was quite small and counted with important contributions from people that were investigating language processing and learning before or in parallel to music-related topics, which made sense the moment I discovered that music and language abilities are pretty much intertwined in our brain structure and functional organization. Music and language are complex and multi-modal activities with a strong base in auditory-motor functions that allow communication between individuals, as well as the expression of feelings and thoughts (Fitch, 2010; Verga & Kotz, 2013). Previous research has described multiple similarities between these two activities (Besson, Chobert & Marie, 2011; Magne, Schön & Besson, 2003; Schön et al., 2010; Tillmann, 2012). Both music and language require the segmentation or chunking of an auditory stream into individual events; the focus on the timing and ordering characteristics of those events (as well as the storage of all this information in short-term memory); the processing of relations, structure, frequency of occurrence and co-occurrence of the individual events; and the online integration of each incoming event into the structure of the context (Tillmann, 2012). Moreover, the knowledge regarding the cultural traits that linguistic and musical systems show and that allows the perceiver to create expectations that help in the processing of future events, is in both cases an implicit acquisition through mere exposition to the perceiver's context (in language: Gomez & Gerken, 2000; Pacton, Perruchet, Fayol & Cleeremans, 2001; in music: Krumahnsl, 1990; Tillmann, Bharucha & Bigand, 2000). As

Patel (2003) proposed and subsequent studies have continued investigating (Hoch, Poulin-Charronnat & Tillmann, 2011; Jentschke, Koelsch, Sallat & Friederici, 2008; Koelsch, Gunter, Wittfoth & Sammler, 2005; Patel, Iversen, Wassenaar, & Hagoort, 2008), music and language share neural resources, mainly for processing syntactic information (i.e., the principles structuring the individual acoustic elements into sequences; Tillmann, 2012).

We decided, thus, to center the focus of this dissertation on questions about individuals differences in music and language abilities and brain structural predispositions, as well as on neuroplastic effects derived from music learning and long-term music practice. We were willing to discover more about the neural basis of music and language processes, which areas could be modified by experience and thus, be crucial for learning linguistic or musical material, and how well can structural neuroimaging methods predict our capabilities in these two domains.

The purpose of this introduction is to draw an overview on neural predispositions, neural substrates and neuroplasticity effects related to the capacities and training in both language and music, as well as on how music and language can and have been used as models in cognitive neuroscience. Then, the main goals of the thesis are explained, followed by the presentation and discussion of the three studies included in this dissertation.

1.2 *Symphony* 'Nature & Nurture'

1.2.1 General considerations

'Which contributes more to the area of a rectangle, its length or its width?' –

Answer by ***Donald O. Hebb*** *(1904 - 1985) when asked by a journalist 'which, nature or nurture, contributes more to personality?'*

As it is the case for any other animals, human behaviour is the product of the combination and interaction between, on the one hand, an inherited package of genes, traits (phenotype) and predispositions, and, on the other hand, the consequence of the environment in which we are raised, in which we learn and train specific abilities and activities, in which we are stimulated, and in which we share experiences with other members of our own and of different species (Gilliam et al., 2000). In a recent review, Plomin, DeFries, Knopik and Neiderhiser (2016) arrive to the same conclusion by elaborating a list revisiting the top 10 replicated findings in behavioural genetics: both genetics and environmental factors importantly contribute to individual differences in psychological traits.

In the behavioural domain, the expression 'nature and nurture' has been used to reflect the relative importance of individuals' innate qualities ("nature") as compared to individuals' personal experiences ("nurture") in determining inter-individual differences (Greenspan, Kandel & Jessel, 1997). There has been an intense debate around this concept, from pure behaviourist and environmental views starting in 17th century (i.e., John Locke's "tabula rasa" views in 1690), to the almost resolution of the discussion by the 2000s admitting that usually both factors play a role (Carlson, 2005; Moore, 2003; Ridley, 2003). After the success of Darwin's theory of evolution in the second half of 19th century, the focus changed in the early 20th century from the pure heredity to the role of environment (Cravens, 1978). Although after World War I twin studies were started to be used as a tool to decompose the behavioural traits in their genetic and environmental components, in the 1920s and 1930s the school of purist behaviourism was created by John B. Watson (Haggbloom et al., 2002). This view of pure cultural/environmental contribution to behavioural traits remained until 1960s with Ashley Montagu, whose theories allowed no contribution from heredity whatsoever (Montagu, 1968). However, from 1970s onwards, and especially since the 1990s (due to the fact that heritability studies became much easier to perform), the pure behaviourism has been progressively replaced by the now-dominant view: usually, both kind of factors contribute to a given trait (Gilliam et al., 2000; Pinker, 2002; Plomin et al., 2016).

Several types of quantitative methods have been applied to study heritable traits, such as developmental genetic analysis (examining the effects of genes over the course of the human lifespan; Plomin, Fulker, Corley & DeFries, 1997; Plomin & Spinath, 2004), multivariate genetic analysis (that investigates the genetic contribution to several traits that may vary together; Cardon, Fulker, DeFries & Plomin, 1992; Luciano et al., 2004), or extreme analysis (studying the link between normal and pathological characteristics; Harrison & Owen, 2003). In the specific case of genetic and environmental interactions that may affect brain structures, imaging genetics methods have been searching for the genetic markers involved in normal brain development and brain structural characteristics (see Figure 1.1 as an example, by Johansen-Berg, 2010). Moreover, previous research has also described markers that mediate the correlations between structural properties (volume of grey matter or microstructural organization of white-matter pathways) and some behavioural traits (Lenroot et al., 2009). As an example in white matter (WM) architecture, Chiang and collaborators (2009) found that genetic

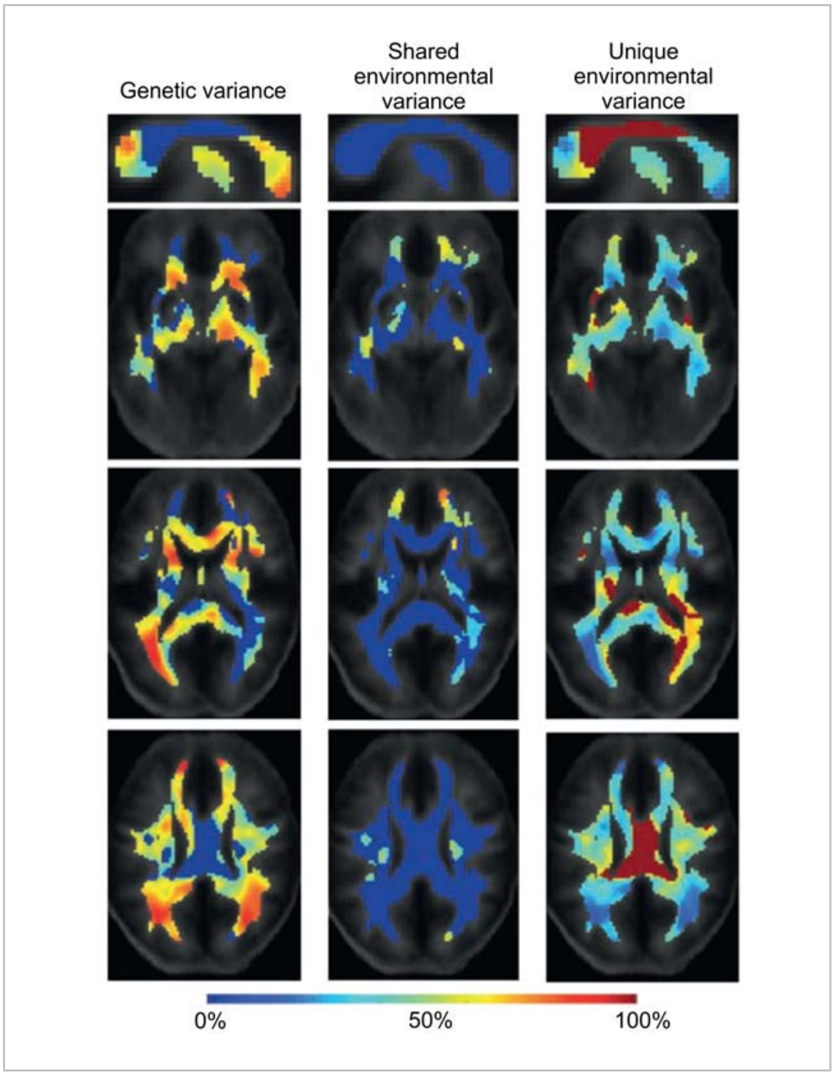


Figure 1.1. Genetic and environmental influences in variations of FA in different white-matter regions. Left column shows purely genetic influences in widespread areas, middle column depicts the shared environmental influences, and right column shows the purely environmentally-explained variation (mainly in the body of the corpus callosum). [Adapted from Johansen-Berg (2010)].

factors mediate the correlation between intelligence quotient and FA in several regions and fibre tracts of the brain (such as bilateral frontal and parietal lobes, the cingulum, the superior fronto occipital fasciculus or the corona radiata, among others). Later, these authors (Chiang et al., 2011) found moderate but significant modulatory effects of age, gender, intelligent quotient (IQ) and socio-economic status on the heritability of WM architecture and integrity (heritability was higher in those individuals with higher socio-economic status, and genetic factors explained more than 800% of the FA variability in the thalamus, genu of the corpus callosum, posterior internal capsule and superior corona radiata for people with high IQ). In another study focused on WM microstructure, variations in a gene linked to depression (i.e., the serotonin transporter gene-linked polymorphic region) were described to be inversely correlated with FA values in the left uncinate fasciculus region (Pacheco et al., 2009). Another investigation by Konrad and colleagues (2009) found that individuals with alterations in the genes codifying for the Neurregulin 1 (ErbB4), which is related to schizophrenia, showed less FA in the temporal lobe and increased reaction times in a selective attention/working memory task. Another study with individuals presenting a genetic risk for schizophrenia (variations in the microRNA-137 host gene), observed a relationship between the presentation of these modifications and reduced grey matter (GM) concentration in occipital, parietal and temporal lobes (Wright et al., 2016).

From a more behavioural point of view, there have been several reports describing a widespread genetic contribution in the observable differences found across subjects in several domains. Bouchard and colleagues have claimed that DNA heterogeneity explains to a great extent the human individual differences in the effects of diet, nutrition and alterations in energy balance (Bouchard, 2008; Bouchard & Ordovas, 2012), as well as in exercise behaviour, cardiovascular and metabolic adaptation to exercise, and responsiveness to regular exercise (Bouchard, Rankinen & Timmons, 2011). And regarding more psychological features, Buss & Plomin (in Goldsmith et al., 1987) stated back at the end of 1980s that environmental factors have received more attention that the evidence was warranting, arguing that genetics could greatly account for variability in personality and psychological features, such as temperament which they described as a set of personality traits that are necessarily inherited. Plomin and collaborators later described an important influence of genetics also on other cognitive domains such as reading performance and sentence comprehension (Plomin, Shakeshaft, McMillan & Trzaskowski, 2013), as well as in second language acquisition abilities (Rimfeld, Dale & Plomin, 2015).

However, we should take into account the concept of epigenetic changes (I will give more details regarding this topic later in this introduction, see section 1.2.2). As Fitch commented in his work on language evolution (2010), epigenesis is nature *via* nurture: the products of gene-expression regulate themselves and other genes in a complex interaction that depends and is influenced by environmental experiences and traits (Fitch, 2010). The context, the environmental stimuli we encounter, the experiences we live and the learning of diverse skills over a lifetime can modify the structure of our brains and the genetic expression. For example, in a smart research with adoptees (age of adoption < 6 months; age-range of the adoptees at the time of the experimental procedure: 18-45 years), Riggins-Caspers, Cadoret, Knutson and Langbehn (2003) controlled the psychopathology risk inherited from birth parents and the harsh discipline experienced from adoptive parents, and found that the environmental factors impacted the degree to which genetic predispositions to aggressive and conduct-disorder traits influenced the final behaviour in the adoptees. Previously, Caspi and collaborators (2002) studied MAOA (monoamine oxidase A) polymorphisms in relation to the effects of parental maltreatment, in order to explain why some children suffering from maltreatment develop conduct disorders, antisocial personality symptoms, or become violent offenders, and others do not. MAOA gene metabolizes neurotransmitters such as norepinephrine and serotonin, whose alterations have been linked to aggressive behaviour (Caspi et al., 2002). Thus, Caspi et al. (2002) found that maltreated children with a genotype encoding for high levels of MAOA expression were less likely to develop antisocial problems and become violent offenders.

Following the ideas by Scarr and McCartney (1983), the environment also plays a role in reinforcing the "choices" that the genetically-determined skills drive the individual to do. These authors described a specific type of genetic-environmental interaction, the evocative type which is based on the responses that the social environment of the individual is providing during development. Importantly for the present work, social interaction is a crucial aspect both in music and language training. On the one hand, musical behaviour is a fundamental part of human experience and it frequently involves interaction with others: (i) lullabies and action songs are an important and enjoyable form of social interaction during childhood; (ii) non-musicians can synchronize both at a motor and at an emotional level in daily life activities related to music (such as assisting to a concert, listening to the radio or being in the audience of a football match); (iii) musical education generally includes band or orchestra practice in which the training is enriched and social communication and interaction are crucial; and (iv) there is evidence that music can be used as a facilitator for communication and social interaction in Autism disorder (Molnar-Szakacs & Heaton, 2012; Overy, 2012). On the other hand, language experience is also tightly linked with social interplay: (i) interaction between partners is the basis of any type of communication; (ii) interactions with a caregiver are necessary for first language acquisition in infants and children; and (iii) social interaction has been described to facilitate L2 acquisition as well (see review by Verga & Kotz, 2013).

In summary, nowadays we know that both nature and nurture drive the development of most human behaviours: behavioural phenotypes are the result of gene expression in concrete environments, and the expression of these genes changes throughout the life of the organism in response to environmental stimuli (Bailey et al., 2015). Since both genetic and environmental factors play a role in determining several behavioural and personality outputs, specific models to study the interaction between those factors are necessary. In order to individualize interventions, in pedagogical, public health and rehabilitation domains, it is necessary to recognize the existence of inter-individual variability, as well as to decipher to which extent the genetic and environmental factors contribute to this human individuality (Bouchard et al., 2011). In the pathway to disentangle these gene-environment contributions, experts of different disciplines have been studied as models of neuroplasticity (i.e., athletes, Del Percio et al., 2009; chess players, Hänggi, Brütsch, Siegel & Jäncke, 2014), as examples of brain predispositions and of the interaction between nature and nurture phenomena (see reviews by Johansen-Berg et al., 2010, and Zatorre, 2013). Among these expert populations, musicians (Jäncke, 2009) and bilinguals (Tao, Marzecová, Taft, Asanowicz & Wodniecka, 2011) appear as excellent models due to (i) their specific training and sustained practice over long periods of time, in tasks recruiting several cognitive activities; (ii) the developmental context in which these activities are usually started to be practiced (music and language training start, in most of the cases, during childhood); (iii) the transfer of the neuroplastic effects from practiced functions to other unrelated and somewhat distant functions (i.e., from music to language -Wong, Skoe, Russo, Dees & Kraus, 2007- or general intelligence and working memory -Schellenberg, 2004-, and from language mainly to executive functions -Bialystok, Craik, Klein & Viswanathan, 2004–); (iv) the open issue regarding whether the talent to play and master an instrument or learn new languages is innate or not. Musicians and bilinguals could help us to better understand the combination and interaction between nature and nurture phenomena (for example, until which point someone with a specific predisposition towards auditory discrimination could benefit from musical practice).

1.2.2 Nature: Structural and functional predispositions

Every human being is aware of the diversity of abilities and aptitudes each one of us possesses. Everybody realizes very soon in life how some people is, for example, gifted for writing but not for singing, for dancing but not for doing crochet, for learning a new language but not for sports, etc. As a matter of fact, important differences between individuals have been reported in the performance of several behavioural activities (i.e., verbal abilities –Johnson, Ladefoged & Lindau 1994; Zatorre, 2013-, spatial abilities –Draganski et al., 2004; Maguire, Frackowiak & Frith, 1997; Maguire, Maguire, Woollett & Spiers, 2006–, perception –Gazzaniga, Ivry & Mangun, 2014; Herholz, Halpern & Zatorre, 2012-), as well as in brain structure and function (Herholz, Coffey, Pantev & Zatorre, 2015; Hu et al., 2012; Johansen-Berg, 2010; Reiterer et al., 2011; Zatorre, Fields & Johansen-Berg 2012; Zatorre, 2013). These individual differences might be explained by genetic predispositions and neuroplasticity mechanisms triggered by the environment and lifetime experiences (Champagne, 2010; Green & Bavelier, 2008; see review by Zatorre, 2013). Predispositions occur when the genetic background influences in a crucial and determining way the development of a certain trait in an individual (Blackburn & Lehman, 2015). They are inherited and behaviourally translated into special capacities with which one is born to learn specific functions or perform some activities (Fitch, 2010). There are some "general human predispositions", such it would be the predisposition to learn the language of the community in which each human being is raised (Fitch, 2010), or the auditory circuit already established for processing musical information in neonates (1 to 3-day-old babies showed an adult-like functional pattern of music processing as well as sensitivity to music violations, Perani et al., 2010). Research in genetics have been trying to estimate how much variation in different phenotypic traits is due to genetic variation among individuals of a studied population (compared to the other measured factors of variation in a trait, the environmental ones), by calculating the statistical heritability (Wray & Visscher, 2008). Nowadays, we know that most behavioural traits are determined by several genes interacting between them and being also affected by environmental factors (i.e., they are multigenic; Gilliam, Kandel & Jessel, 2000).

There have been heritability studies focused on genetic susceptibilities to develop particular neurologic and psychiatric diseases, such as Schizophrenia (Gottesman, 1991) or Huntington disease (Warren, 1996). In addition, heritability has been described for some human behavioural traits, shedding light to the extent in which personality, intelligence or certain performing capacities may be influenced by genetic factors (Bailey, Patterson & Fairbanks, 2015; Finkel, Reynolds, McArdle & Pedersen, 2005). In the specific case of language, specific pathological cases have helped to determine the important role of the gene FOXP2 (Hurst, Baraitser, Auger, Graham & Norell,1990; Lai, Fisher, Hurst, Vargha-Khadem & Monaco, 2001) and of the locations at chromosomes 16, 19 and 13 (i.e., SLI1, SLI2, SLI3) in the normal acquisition, development and articulation of language, remarking the importance of genetic influence in such a complex and culturally-related behaviour (Pásaro-Méndez & Fernández-García, 2005). Regarding music abilities, there are a few investigations showing a genetic contribution to general musical aptitude. Specifically, musical abilities have been related to genes previously described to be involved in inner-ear development, auditory perception, cognition and memory, reward mechanisms, song perception and production in songbirds (Liu et al., 2016), associated to the development of Dyslexia (Pulli et al., 2008), or involved in brain organisation (Park et al., 2012). Furthermore, Drayna, Manichaikul, de Lange, Snieder and Spector (2001) have shown a strong genetic effect but no environmental effect on pitch perception. In the same line, Ullén, Mosing, Holm, Eriksson & Madison (2014) have observed a clear genetic influence with little environmental contribution for music perception and music training (Mosing, Madison, Pedersen, Kuja-Halkola & Ullén, 2014; Ullén et al., 2014). A recent investigation by Seesjärvi et al. (2015) describes a more complex pattern, concluding that music skills and music perception are complex phenomena affected by both genetic and environmental factors (i.e., pitch discrimination ability seems primarily determined by genetic influence, while the perception of musical tonal and metric structures may be more influenced by environmental aspects).

In addition to the genetic material *per se* and the dichotomy between genetic and environmental factors, it is important to note that the environment might relevantly change the way in which our genes are expressed. Some external factors can switch genes on and off or affect how the cell reads the genes, without altering the nucleotide sequence or DNA (DesoxyriboNucleic Acid) (Moore, 2015). Specifically, the DNA sequence can be methylated (cytosine nucleotides are converted to 5-methylcytosine) and the histone proteins around which the DNA is wrapped in the cell nucleus, can be modified (i.e, by processes like methylation, acetylation and ubiquination) (Champagne, 2010). These alterations are called epigenetic processes. They include alterations in the state of expression of a gene that does not involve a mutation (silencing, for example), but that could be activated and inherited in the absence of the signal or event that initiated the change (Ledford, 2008; Spector, 2012). Epigenetic mechanisms are especially instantiated in the brain during early-life experiences (Champagne, 2010; Kubota, Miyake, Hirasawa, Nagai & Koide, 2010), and have been related to later-in-life behaviours like maternal care or endurance during physical exercise (Champagne, 2010; Sharples, Stewart & Seaborne, 2016). See Figure 1.2 for an illustration of the possible factors involved in epigenetic processes.

Although the study of the human genome raised the expectations of the scientific community at the beginning of the 2000s regarding the understanding of genetic predispositions, there is not a single gene that has been found to explain irrefutably the individual differences in any kind of complex behaviours (Pásaro-Méndez & Fernández-García, 2005). Previous research leads to the conclusion that one should be cautious when speaking about genetic influences, since it is also necessary to be aware of the intertwined web of genetic processes that play a role in codifying the polygenic heritability (i.e., controlled by the interaction of more than one gene) of a disease or behaviour (Gilliam et al., 2000; Pásaro-Méndez & Fernández-García, 2005; for a review on behavioural genetics, see Plomin et al., 2016).

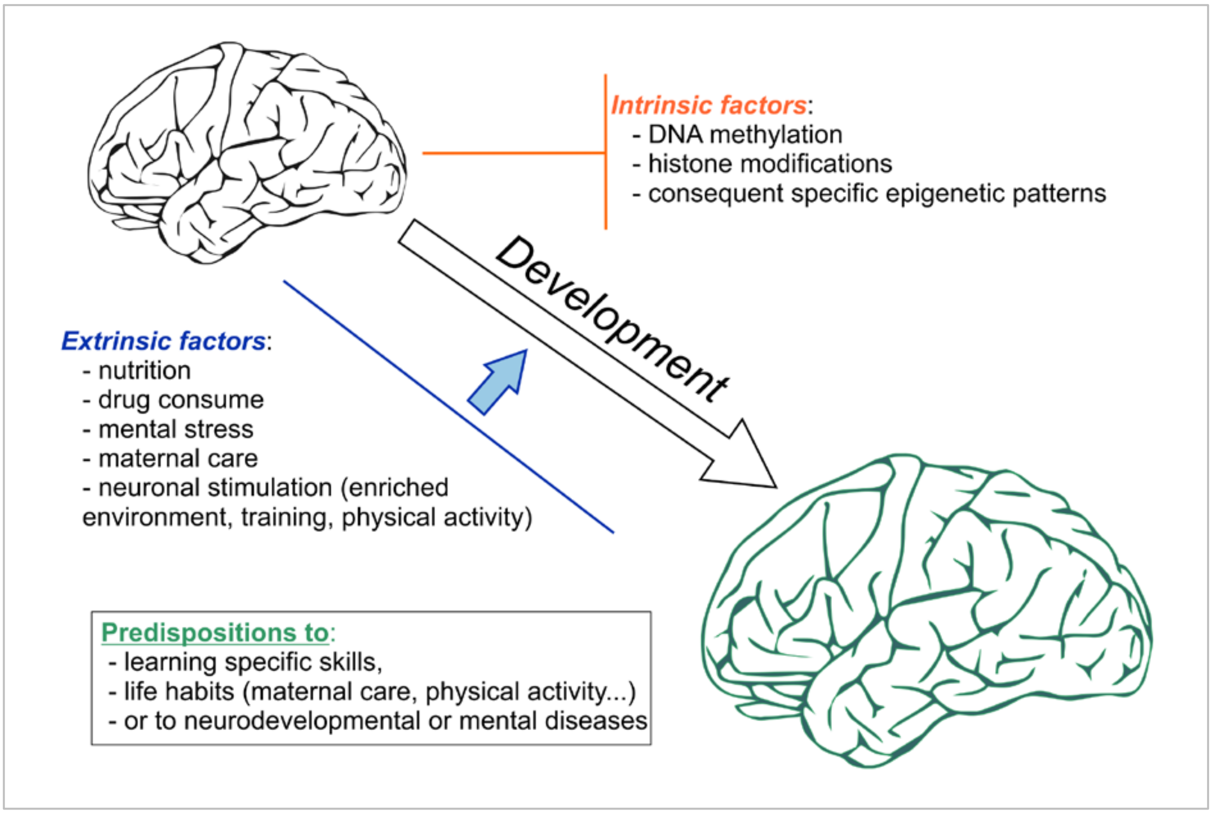


Figure 1.2. Scheme of the possible epigenetic factors divided in intrinsic and extrinsic ones. Extrinsic factors are supposed to affect intrinsic mechanisms, in order to instantiate the potential changes in the reading of the genetic material. [Figure adapted and modified from Kubota et al. (2010), with ideas from Champagne (2010); Gómez-Pinilla (2008); Romani, Pistillo & Banelli (2015); and Sharples et al. (2016) as well].

In the specific field of cognitive neuroscience, brain structure and function have been reported to differ importantly between individuals (Johansen-Berg, 2010). For instance, recent human-brain MRI research has shown that inter-individual variability in several cognitive functions and behaviours can be predicted from the local structure of GM and WM, when assessed via voxel-based morphometry or DTI techniques (Càmara, Rodríguez-Fornells & Münte, 2010; Kanai & Rees, 2011). Specifically, regarding sensory perception, Seither-Preisler, Parncutt and Schneider (2014) have recently described in children aged 7-9 years how the grey matter structure of the right auditory cortex explains the individual differences in pitch-perception and discrimination tasks. Rodríguez-Herreros and colleagues (2015) have observed predisposing factors in motor-control functions combining voxel-based analysis of WM and a repetitive transcranial magnetic stimulation (rTMS) protocol. These authors created a transient disruption of the neural processes involved in on-line motor adjustments by applying rTMS to the medial intraparietal sulcus. They observed that those subjects with higher fractional anisotropy (FA) values in the superior longitudinal fasciculus (specifically, branch II) suffered a smaller degree of TMS-behavioural affectation in a reaching (motor correction) task (Rodríguez-Herreros et al., 2015). In addition to the predictive value of brain structural imaging, functional MRI data has also given some insight regarding inter-individual differences. A recent study by Herholz and colleagues (2015) found that the pre-training activity in areas encoding auditory information and involved in some aspects of motor control (i.e., right Heschl's gyrus, right hippocampus, left premotor cortex and caudate nucleus bilaterally), predicted subsequent learning rates in a 6-weeks piano training protocol. As another example, increased activity in medial prefrontal cortex and connectivity between medial prefrontal and hippocampal regions during the encoding period of an emotional associative memory task have found to be predictive of the behavioural outcome in this task (i.e., reduced memory retrieval for associations containing a negative valence component) (Berkers, Klumpers & Fernández, 2016). Besides, Huang, Obara, Davis, Pokorny and Northoff (2016) have recently found that functional connectivity in the middle prefrontal cortex during rest predicted the level of self-related thoughts and reflections as assessed via a psychological scale (i.e., Revised Self-Consciousness Scale). Finally, in a language-related paradigm, López-Barroso et al. (2013) have found that both the microstructural organization of the left arcuate fasciculus (the white-matter bundle connecting superior temporal, inferior frontal and inferior parietal regions) and the strength of functional connectivity between left temporal regions and left inferior frontal areas correlated with the performance in a word-learning/speech segmentation task.

In close relationship with the inter-individual differences, arises the concept of "talent", an interesting and exceptional capacity that only a few individuals possess in one or several domains of learning (from music to mental abilities to gymnastics, Baláková, Boschek & Skalíková, 2015; Christiner & Reiterer, 2013; Pion, Lenoir, Vandorpe & Segers, 2015). Talent makes reference to a special efficiency in learning or a disposition toward good performance in the activities involved in learning a specific function or activity (Jilka, 2009). As such, talent might be seen as a special innate predisposition that will determine the way in which the talented individual learns. As an example of talent in music, Sowinski, Dalla Bella and Laskowska (2009) reported the case of a 5-year-old drummer who showed outstanding sensorimotor synchronization and anisochrony detection abilities in comparison to age-matched and adult non-musician controls. Moreover, in parallel to talent, there is creativity, a special trait that allows human individuals to display an optimal functioning in different domains (Simonton, 2000). The acquisition of creative potential requires a combination of intellectual and other genetic predispositions with some laborious training, leading to expertise in a specific field (Simonton, 2000).

But as Johansen-Berg asks rhetorically in her review from 2010 (talking specifically about white matter properties and organization): "To what extent does the physical state of our brain network determine our skills and abilities? If our behaviour is influenced by the condition of our fibre pathways, is this relationship dictated by our genes, or modifiable by experience?". As Zatorre argued (2013), "we know that the nervous system should adapt its structure and function in order to optimize its responses to the environment that it is experiencing, but the initial state of the brain before these adaptations and changes take place is not the same for all individuals". In other words, it seems that the genetic background of an individual would define some traits that would be translated as inter-individual differences at the starting point of any learning process. Furthermore, it is possible that individuals with an inherent talent or skill look for practicing those activities that reward their particular skill set (Green & Bavelier, 2008). In addition, it seems that environmental experiences could also modify the expression of our genetic background, by potentiating or attenuating some predispositions (via epigenetic processes). In line with all these concepts, Scarr and McCartney (1983) proposed an interesting framework for gene-environment interactions in which the genetic background is driving human experience, but experiences are also necessary for development. These authors posited that it is likely that particular genotypes predispose some people to receive certain kinds of parenting (passive genotype-environment interactions), evoke certain responses from others (evocative gene-environment correlations, reinforcing the directions that development has taken), and seek out environments they find compatible with motivational, personality and intellectual aspects of their genotypes (active genotype-environment interactions) (Scarr & McCartney, 1983). In addition, these three types of genetic-environmental interactions change over normal development, with more weight of the passive kind during infancy and childhood, and more importance of the evocative and active type later in adolescence (Scarr & McCartney, 1983).

1.2.3 Nurture: Neuroplasticity

“Todo hombre puede ser, si se lo propone, escultor de su propio cerebro.”

Santiago Ramón y Cajal

Our nervous system possesses the ability to reorganize its structure, function and connectivity in order to make a proper response to the intrinsic and extrinsic stimuli encountered throughout a lifetime (Bayona, Bitensky & Teasell, 2005; Cramer et al., 2011;

Kolb & Whishaw, 1998; Zatorre, 2013). This capacity, known as neuroplasticity, affects many levels, including molecular, cellular, systemic and behavioural; and, in addition, it can take place during normal development, in response to a disease or the environment, in relation to learning or as a consequence of a specific training or therapy (Cramer et al., 2011). Although neuroplasticity mechanisms tend to decrease in older adults, this adaptive capacity of the brain has been described to be present over the course of the typical lifetime (Freitas, Farzan & Pascual-Leone, 2013).

Brain capacity seems to depend not on the number of neurons or the cortical surface area, but on the number of functional connections (since this is the measure that crucially differs between humans' and other species' brains) (Bayona et al., 2005). As Kolb (2003) described, in a healthy brain the number of functional connections continue to increase until very old age, compensating for the gradual loss of neurons. Hence, brain plasticity is mainly mediated by creation and modification of synapses and not through the creation of new neurons (Bayona et al., 2005), although neurogenesis in some restricted areas of the brain (i.e, olfactory bulb and hippocampus) has been also reported in adult vertebrates (Kolb & Whishaw, 1998; Kornack & Rakic, 1999; Sweatt, 2016; for a review in neuroplasticity see Kolb & Muhammad, 2014). A connection between brain function and brain anatomy is generally expected (Zatorre et al., 2012), although interpreting MRI changes and measurements in biological terms continues to be challenging (Johansen-Berg, Sampaio Baptista & Thomas, 2012) (but see the rest of this section and section 1.4.1, for more details on possible molecular and cellular mechanisms explaining the structural findings detected by MRI methods).

Despite the fact that there has not been a clear consensus in the last years of how are these newly-created functional connections translated into structural changes and that there is not a clear relationship between most MRI measurements and the underlying tissue properties (Johansen-Berg et al., 2012), a combined approach with neuroimaging and neuropsychological data can help us to identify the relationship between function and anatomy. As an example, Froudist-Walsh and collaborators (2015) reported interesting findings in adults who suffered peri-natal brain injury (PBI). These authors found that adults with PBI showed reduced volume in the dorsal cingulum in association with functional alterations in the perisylvian cortex: cingulum volume and perisylvian activity were negatively correlated, and inhibition of perisylvian regions was correlated with improvements in working memory performance (Froudist-Walsh et al., 2015). These results are thus interpreted as a form of compensatory mechanisms in order to cope with behavioural requirements of the environment (working memory), despite the brain damage suffered very early in life (Froudist-Walsh et al., 2015). As a matter of fact, Kolb and Muhammad (2014) commented on a recent review how the term 'recovery' after brain damage, encompassing all the plasticity mechanisms that take place after brain injury, should be seen and replaced by terms such as adaptations and compensations of the remain system to the new situation. Another example of functional/structural relationship can be found in an interesting research carried out by Makin and colleagues (2013) examining individuals with congenital and acquired hand-absence. Using a motor fMRI task and DTI data, these authors found an increased activation of the deprived sensorimotor cortex paired with and determined by the limb-use strategy (use of the contralateral intact limb vs. adaptation and use of the residual arm) adopted by the individuals, rather than by the age of deprivation (Makin et al., 2013). Moreover, activation caused by intact-hand movement in the deprived cortex was positively correlated with FA values in several clusters distributed among the CST and the IFOF (Makin et al., 2013). These authors suggest that longer-range plasticity (from the intact hand representation to the deprived, contralateral hand representation) may elicit white-matter change, and that plasticity mechanisms in the affected cortex are driven by the over-use of one of the limbs, regardless of the age of acquisition of hand-loss (Makin et al., 2013).

Brain plastic changes, at a molecular level, follow different time-window ranges. There can be *functional alterations* related to changes on how the information is encoded and communicated through the neurons, which are rapid alterations that only last for some hours (Karni et al., 1998). These s*hort-term changes* involve the expression of early genes, modifications in the synaptic efficacy and long-term potentiation/long-term depression (LTP/LTD) processes (Bayona et al., 2005). Examples of short-term changes are the uncovering and activation of latent but existing connections (Jacobs & Donoghue, 1991; Karni et al., 1998), by an increment in the number of neurotransmitter receptors in the postsynaptic cell, or by the expansion of the dendritic surface contact area (i.e, creation of new dendritic spines) (Bayona et al., 2005). It is important to mention the case of creation and reorganization of dendritic spines, a plastic mechanism showed after several types of experiences such as tactile stimulation, drug consumption or exposure to complex environments (Kolb & Muhammad, 2014; Muhammad et al., 2011; Richards et al., 2012). As an example, Xu and collaborators (2009) showed that training mice in a forelimb reaching task induced fast (within an hour) formation of postsynaptic dendritic spines on the output pyramidal networks, in the contralateral motor cortex (see also Fu & Zuo, 2011). Moreover, this mechanism has been evidenced in studies in which enriched environments and motor-training were used as rehabilitative approaches after brain damage (Biernaskie & Corbett, 2001; for a review see Kleim & Jones, 2008).

Associations between pre- and post-synaptic cells rely upon a mechanism that detects coincidental activity between them, in which N-methyl-D-aspartate receptors or NMDAR, a subtype of glutamate receptors, play a crucial role (Collingridge, Kehl & McLennan, 1983); importantly, NMDA-plasticity-related changes after learning have been observed across diverse phylia, both in invertebrates and mammals (Kolb & Muhammad, 2014). Shifts in the neurotransmitter or enzyme that an axon produces, or changes in the excitability of the post-synaptic cell, can modify the nature of the pre- and post-synaptic cells configuration and communication, eliciting synaptic modifications (Bayona et al., 2005; Sweatt, 2016). These alterations are due to the activation of genes involved in cell-structure via LTP/LTD phenomena (Bayona et al., 2005). LTP improves the synaptic efficiency and is induced by coincidental activity of pre- and post-synaptic elements, which brings a facilitation of chemical transmission between both cells (mainly studied in relation to NMDAR, Malenka & Nicoll, 1999; Nicoll & Roche, 2013; Sweatt, 2016; Toni, Buchs, Nikonenko, Bron & Muller, 1999). LTP can be triggered by a change in the use of neural pathways due to experience (alterations in the sensory inputs or motor outputs during a movement, for example), and has been described to mediate different types of associative learning, spatial learning, and broad adaptive behavioural modifications in the CNS in mammals (Sweatt, 2016). LTD is a long-lasting decrease in synaptic efficiency and it is produced by a prolonged mismatch between pre- and post-synaptic action potentials (Etkin et al., 2006; Malenka & Nicoll, 1999; Sweatt, 2016). LTD has been assumed as a homeostatic mechanism to ensure that synapses are not saturated by learning, although it may mediate learning in itself by promoting forgetting processes or behavioural extinction mechanisms (Cooke & Bliss, 2006). LTP/LTD processes can affect a single synapse, while other modifications such as the changes in excitability affect all the synapses in a given neuron (Sweatt, 2016).

On the other hand, there can be *anatomical alterations* that imply structural changes in the neural architecture, which require more time for full expression although they would last not just for few hours but even days (i.e., long-term changes) (Karni et al., 1998; Kolb & Whishaw, 1998). *Long-term alterations* include expansions in dendritic arborization, dendritic-spine density, and a boost in the number of synapses per neuron (in summary, the consolidation of several stable new connections/synapses, Bayona et al., 2005; Kolb & Whishaw, 1998). In addition to the creation of these new synapses (i.e., synaptogenesis), creation of new neurons (i.e., neurogenesis) from neural stem cells and progenitor cells may take place in some brain regions (specifically, in the olfactory bulb and the hippocampus) (Kolb & Whishaw, 1998; Kornack & Rakic, 1999; Sweatt, 2016). A possible timeline of plastic changes in the brain can be seen in Figure 1.3.

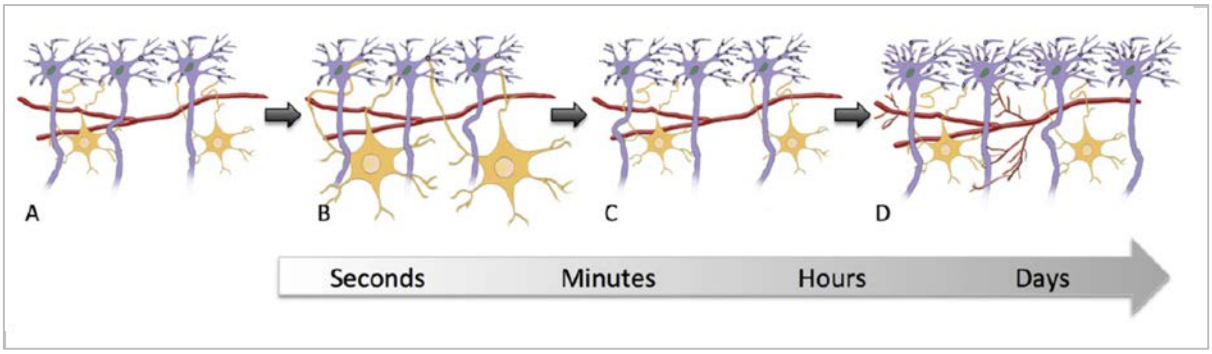


Figure 1.3. Possible timeline of plastic changes in brain tissue. Neurons are in purple, blood vessels in red and astrocytes in orange. A) Baseline state. B) Swelling of the astrocytes due to an increase in neural activity (this process can take place over a course of seconds to minutes). C) Synapses (black circles on the dendrites) and their associated dendritic spines can be formed and modified over a period of minutes to hours. D) More complex alterations such as dendritic sprouting, neurogenesis, or angiogenesis need a longer period of time (i.e., days to weeks). [Adapted from Johansen-Berg et al. (2012)].

At systems' level, these cellular modifications are expressed as functional or structural changes within different regions of the brain, which will have consequences at a behavioural level. As an example, Scheibel and colleagues (Jacobs, Schall & Scheibel, 1993; Jacobs & Scheibel, 1993) found a relationship between the dendritic size in the neurons from Wernicke's area and the level of education, in a post-mortem brain examination. In this case, an interesting issue regarding whether the education is the cause or the consequence of this dendritic difference arises, since as discussed in the previous sections both experience and genetic predispositions play a crucial role in our brain structure and function and our behavioural performance. More recent reports still point out the limited validity of cross-sectional studies in order to discern between brain anatomical features caused or being the consequence of different experiences (Zatorre et al., 2012; Zatorre, 2013). Brain plasticity is also promoted (both in humans and other animals) by some life habits such as physical activity or routines like intermittent fasting, both examples implying a challenge to our brains that would be overcome by facilitation of neurogenesis and synaptic plasticity (i.e, these habits would elicit the releasing of neurotrophic factors -such as Brain derived neurotrophic factor or BDNF-, which would in turn mediate neural plasticity) (Champagne, 2010; Cherif, Roelands, Meeusen & Chamari, 2016; Green & Bavelier, 2008).

Besides everyday routines and lifestyle, neuroplasticty after learning and experience has been extensively studied. Experience elicits an important reorganization of the brain, and this not only improves the performance in the experienced domain (such as motor or sensory functions, for example), but also boosts the future learning potential of the individual (Bayona et al., 2005) (I will expand this issue in section 1.4).

1.2.4 Sensitive periods and impact of the age of-onset of training

I would like to continue now with the concept of sensitive periods, or whether the experiences we have in life have different effects depending on the developmental state in which our brain is. The existence of a sensitive period, a limited time during normal development in which the effect of experience on brain function is particularly strong (Hensch, 2005; Huttenlocher, 2003) and can contribute to long-lasting changes in brain structure and function as well as in behaviour (Penhune, 2011), have been proposed for several brain functions and skills. The concept of critical period was first proposed for language functions (the Critical Period Hypothesis, described by Penfield and Roberts, 1959; followed by assumptions in the same line by Lenneberg, 1967), assuming a crucial time window for the acquisition of segmental phonology, inflectional morphology and syntax. This theory was then supported by experiments in primary sensory systems. In the visual domain, for instance, several experiments of monocular deprivation in animals revealed a time window in which the visual cortex needs to receive visual input from the environment to complete its development; otherwise, the eye that was occluded would be forever blind, even after the occlusion is removed (Hubel, Wiesel & LeVay, 1976; Shatz & Stryker, 1978; Wiesel & Hubel, 1963). These experiments thus evidenced a strict period of time during which experience with the environment provides crucial information without which normal development of that system is not possible, permanently altering its performance (Hensch, 2005). However, in the last decades the concepts of neural plasticity, neurogenesis and brain repair have been redefined, and the current picture of the adult brain is more dynamic than previously thought (DeFelipe, 2006). As a matter of fact, a recent research by Kalia and collaborators (2014) showed that the visual system exhibits some residual plasticity, even after blindness has extended beyond the critical periods. These authors studied contrast sensitivity acquisition on early-onset blind subjects (beginning before 1 year of age and lasting 8–17 years) after removal of bilateral cataracts, and observed that these patients were able to develop this visual feature, which is crucial for basic spatial vision (Kalia et al., 2014). These and other previous results have changed the point of view of brain malleability, shedding some doubts about the rigid interpretation of this sensitive time window hypothesis, at least for some perceptive functions as well as for some superior cognitive abilities and skills, such as language and music learning in adults (Penhune, 2011; Rodriguez-Fornells, Cunillera, Mestres-Missé & de Diego-Balaguer, 2009). Hence, although research has to advance our knowledge on this matter yet, it is quite assumed that there is a somewhat limited time window in normal development during which experience and training can modify the brain in a particularly strong way (i.e., sensitive period). In this vein, it has been reported that extensive musical or language practice during childhood and adolescence might have a strong effect on the development of brain structures (Klein, Mok, Chen & Watkins, 2014; Penhune, 2011).

In a pioneering study in the field of the neuroscience of music, Schlaug, Jäncke, Huang, Staiger & Steinmetz (1995) have showed that professional musicians (pianists and string-players) had a larger anterior half of the corpus callosum compared to a non-musician control group. Interestingly, the differences were driven by musicians who had begun their training before the age of 7 (showing a larger anterior part of the corpus callosum compared to those with a late training onset). In a DTI study with pianists, Bengtsson and colleagues (2005) found that several white matter tracts correlated with the estimated amount of musical practice during childhood (e.g. posterior limb of internal capsule, the isthmus and the body of corpus callosum, and some fibre tracts in the frontal lobe), although the total number of practicing hours was lower in this period than the estimated hours in adolescence and adulthood. In a more recent DTI study, Steele, Bailey, Zatorre & Penhune (2013) have found that early-trained musicians (age of start <7 years) outperformed late-trained musicians (age of start >7 years) in a visuo-motor synchronization task, although early- and late-trained groups did not differ in their years of musical experience, years of formal training or hours of current practice. These authors have observed as well a negative correlation between FA in the posterior mid-body of the corpus callosum (meaning that the earlier the start of musical training, the better the white-matter microstructure in that particular region). The authors interpreted their findings as evidence for a sensitive period, which might take place during the normal development of the corpus callosum between the ages of 6 and 8 years, when the major changes for this structure have been described (Westerhausen et al., 2011). They also hypothesized that training during this sensitive period may induce changes in WM connectivity that serve as a scaffold on which later training can build, enhancing the system (Steele et al., 2013).

In the language domain, besides the Critical Period Hypothesis for L1 acquisition (Penfield & Roberts, 1959), effects driven by the age of onset of L2 training have been also described. Johnson and Newport (1989) have tested on a grammatical judgement task Korean and Chinese speakers who arrived to the United States at different ages. They found that the earlier (younger) these immigrants arrived, the better they performed in the English grammatical tests, leading to the conclusion that the critical period for language acquisition also extends to second language learning. In a more recent investigation comparing early and late bilinguals (cut off for age of exposure = 3 years), Isel, Baumgaertner, Thrän, Meisel and Büchel (2010) observed a stronger involvement of prefrontal cortex for late bilinguals in a cross-language L1-L2 repetition task, evidencing a higher between-languages switching cost in those participants. The authors thus hypothesized that the age at which an individual is first exposed to its L2 might have an effect on the cortical organization of his/her L2. Bilingual individuals have to control which of their languages should they use depending on the context, as well as monitor and control the switching from one language to the other in an efficient way, which requires a constant practice of executive functions. Hence, it is not surprising that improvement on executive functions had been frequently described in bilingualism studies. Tao and colleagues (2011) reviewed previous literature in order to further interpret this executive-functions improvement. When looking at effects of age of acquisition of L2, it seems that late bilinguals may train their executive control functions to a greater extent than early bilinguals, going against the typical description of "early-commencement benefits" (Tao et al., 2011). Moreover, Tao and collaborators (2011) also hypothesized that executive control effects related to age of acquisition might not be driven by biological or maturational factors, but by a set of environmental factors that might cause the early or late start of L2 learning. Despite the lack of awareness on which, maturational (genetic predispositions) or environmental (access to certain activities or social context, for example) factors are driving sensitive period effects the most, recent reports continue to show that the brain may be more prepared to acquire an L2 earlier in life. For instance, Pallier and colleagues (2003) recruited Korean subjects that were adopted in France between 3 and 8 years of age and that had no conscious recollection of Korean language, and compared them with a group of French monolinguals in language perception and comprehension tasks. Behaviourally, adopted subjects were unable to recognize Korean sentences or words better than native French controls. Furthermore, fMRI results showed that there were no differences in brain activation when adopted participants listened to Korean as compared to other unknown languages such as Japanese or Polish, and the cortical regions responding to French were similar to the ones observed in native French controls (Pallier et al., 2003). These authors conclude that the early acquisition of a second language does not necessarily involve different brain systems than those involved in the acquisition of the mother tongue (Pallier et al., 2003). In line with these conclusion, Klein and colleagues (2014) compared a group of monolinguals and a group of bilinguals, the latter one divided in simultaneous bilinguals, early-childhood (4-7 years) and late childhood (8-13 years) age-of-start bilinguals. They found that the age of L2 acquisition correlated with cortical thickness: positively in the left inferior frontal gyrus (IFG) and negatively in the right IFG. Furthermore, the most interesting finding was that monolinguals and simultaneous bilinguals did not differ in any region on cortical thickness measurements, which leads to the conclusion that simultaneous acquisition of two languages may not elicit especial or additional effects on brain development, while learning an L2 later in life can permanently alter brain structures and functions (Klein et al., 2014). This same group recently reported the unconscious maintenance of a lost language in a cohort of Chinese participants adopted into native French families around 1 year of age (mean age of adoption: 12.8 months) by comparing them to a group of French monolinguals and another group of Chinese-French bilinguals (Pierce, Klein, Chen, Delcenserie & Genesee, 2014). The fMRI results of this investigation showed that, when processing lexical tone, both the adoptees and the Chinese-French bilinguals recruited left temporal regions (superior temporal gyrus and planum temporale, suggesting the application during this task of top-down processing of previously learned linguistic categories), while native French subjects recruited right temporal regions (suggesting processing of complex acoustic, non-linguistic, signals) (Pierce et al., 2014). This maintenance is interpreted by the authors as a form of foundation for subsequent language learning that, in the adoptees, was disrupted at an early age when the first language was lost, although it is still evident at a neural level (Pierce et al., 2014). See Figure 1.4 for the depiction of these results.

These previous results support the idea that the central nervous system exhibits greater plastic capacities during early stages of development and maturation periods, contrasting with its limited malleability during adulthood (Bengtsson et al., 2005). Both music and language rely on audio-motor functions, hence a musical or a linguistic experience during normal development of brain structures involved in these functions is expected to change to some extent how these structures will mature. Following the GM maturation sequence described by Gogtay and collaborators (2004), motor and sensory areas may be the first to mature, followed by speech and language regions; the temporal lobe follows an interesting pattern with temporal poles maturing early, the rest of the temporal lobe maturing slowly and later (in an age range between 4 and 21 years), with a specific area in the posterior superior temporal gyrus (STG) that seems to mature last (STG contains the primary auditory cortex, and hence this maturational schedule may give some cues regarding why early musical and linguistic training may have this great power to elicit neuroplastic alterations). Regarding WM maturation schedule, Giedd and collaborators (1999) found a linear increase of WM volume with age, without significant differences among the various lobes. More recent research confirmed this steady increase of WM maturation through childhood and adolescence (Barnea-Goraly et al., 2005), reporting increasing FA values with increasing age in prefrontal regions, internal capsule, the basal ganglia and its connections with the thalamus, the corpus callosum (CC) and the ventral visual pathways. Furthermore, Asato, Terwilliger, Woo & Luna (2010) described in more detail how several WM tracts belonging to intrahemispheric connections (inferior fronto-occipital fasciculus, superior longitudinal fasciculus) and some projection tracts (corticospinal tract and corona radiata) mature earlier in adolescence, while other projection fibers (internal capsule and the tracts connecting striatum and thalamus with prefrontal regions) and association bundles (uncinate fasciculus, corpus callosum) continue the development through adolescence. Nonetheless, more research on this topic is necessary in order to confirm and expand the knowledge regarding these maturational patterns and optimal sensitive periods for learning.

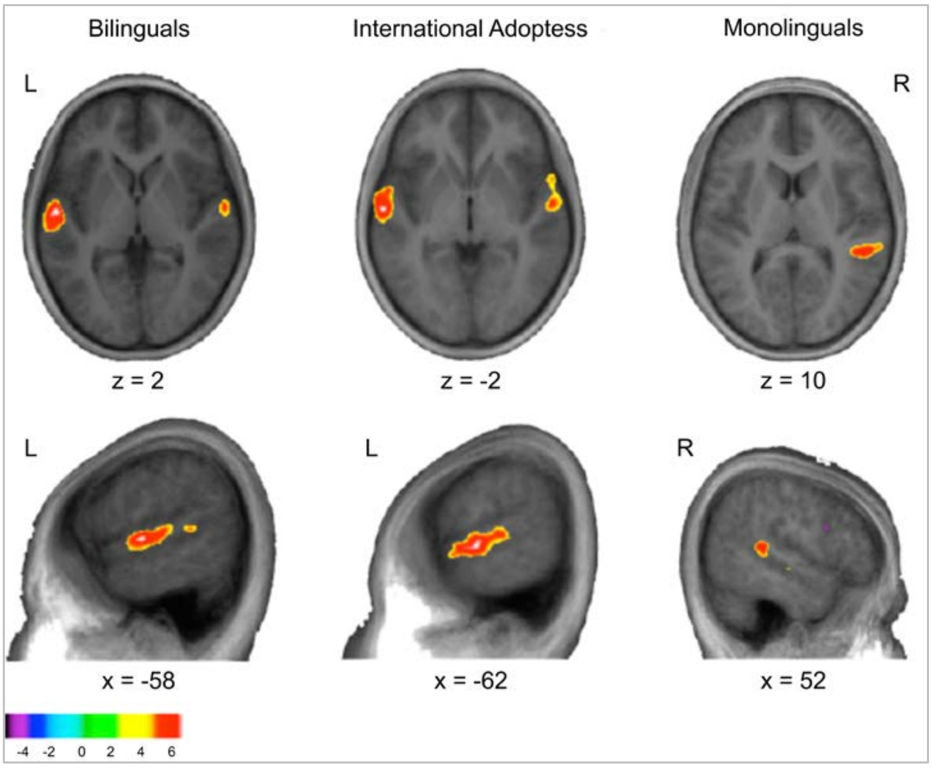


Figure 1.4. Example of the effects elicited by early experiences and sensitive periods. The figure shows the results found by Pierce et al. (2014): when listening to Chinese, French monologinguals activate the right auditory cortex, while both Chinese bilinguals and international adoptees (who had no conscious recollection of Chinese) showed a bilateral activation of superior temporal cortices. This evidences a maintenance of the first language to which adoptees were exposed, despite the fact this language is currently lost at a behavioural level. [Adapted from Pierce et al. (2014)].

1.3 *Sonata* 'From auditory perception to foreign-language imitation and music production'

1.3.1 Language processing

The most accepted neural model for language processing is based on 19th century theories described by Broca, Wernicke and Lichtheim, and revisited by Geschwind during the 20th century (Price, 2012). Wernicke already emphasized the close link between auditory and motor functions in language processing (Wernicke, 1874). As a matter of fact, he highlighted the importance of an anatomical link between the superior temporal gyrus (Wernicke's area), which sustains the acoustic information of words, and the inferior frontal gyrus (Broca's region), in charge of the motor articulation of speech. In this vein, the more recent "motor theory of speech" (Liberman & Mattingly, 1985) and the "mirror neuron system" (Rizzolatti & Arbib, 1998; Rizzolatti & Craighero, 2004; Rizzolatti, 2005) theories describe the phonetic elements as articulatory gestures and representations that are crucial elements to map during perception in order to reproduce the different sounds.

Based on all these concepts, especially regarding the audio-motor integration processes involved in speech perception, there is a predominant view regarding the cortical organization of language: the dual-stream model of language processing. From a functional point of view, this model describes (i) a dorsal stream, left lateralized, responsible of mapping acoustic speech signals (i.e., general auditory perception, related to the spatial localization of the sounds) to their articulatory-based representation (i.e., auditory-motor integration, mapping sound to the muscular action needed to pronounce); and (ii) a ventral stream controlling the mapping of sounds to its corresponding meaning (Hickok & Poeppel, 2000, 2004, 2007; Hickok, Houde & Rong, 2011; Poeppel & Hickok, 2004; Rauschecker & Scott, 2009; Rodríguez-Fornells et al., 2009).

Anatomically, at the cortical level, the *dorsal stream* involves the parieto-temporal boundary and posterior frontal regions, including IFG/Broca's area and premotor regions; the involvement of multisensory integration regions with motor control and motor planning areas explains the role of the dorsal stream in auditory-motor integration and new word learning (Hickok & Poeppel, 2007; Rodríguez-Fornells et al., 2009). On the other hand, the *ventral stream* encompasses the middle and superior temporal cortices, as well as inferior temporal and the anterior temporal pole; the cortical regions involved point out to the role of the ventral stream in mapping sound to meaning and in the creation of novel conceptual structures (Rodríguez-Fornells et al., 2009; Saur et al., 2008). A key region in both streams is the superior temporal gyrus (STG) which has been described (using direct cortical recordings of activity in human subjects) to show a great selectivity to perceive phonetic features and manner of articulation, being both traits crucial in speech processing (Mesgarani et al., 2014). In addition to these more classical cortical regions, subcortical structures play also an important role in language processing, mainly the cerebellum and the basal ganglia (Price, 2012). The cerebellum has been reported to play a role in articulation and word generation (Frings et al., 2006), in motor functions and preparation for vocalisation (Bohland & Guenther, 2006; Murdoch et al., 2010), as well as in timing and rhythm organization of utterances (Ackermann, 2008; Gosh et al., 2008). The basal ganglia, with connections to prefrontal cortex and posterior cortical regions, have been suggested to participate in syntactic processing (Friederici & Kotz, 2003) and in articulatory activity and overt speech production (Bohland & Guenther, 2006; Koelsch et al., 2009). Figure 1.5 shows the cortical and subcortical GM structures reported to be involved in language processing.

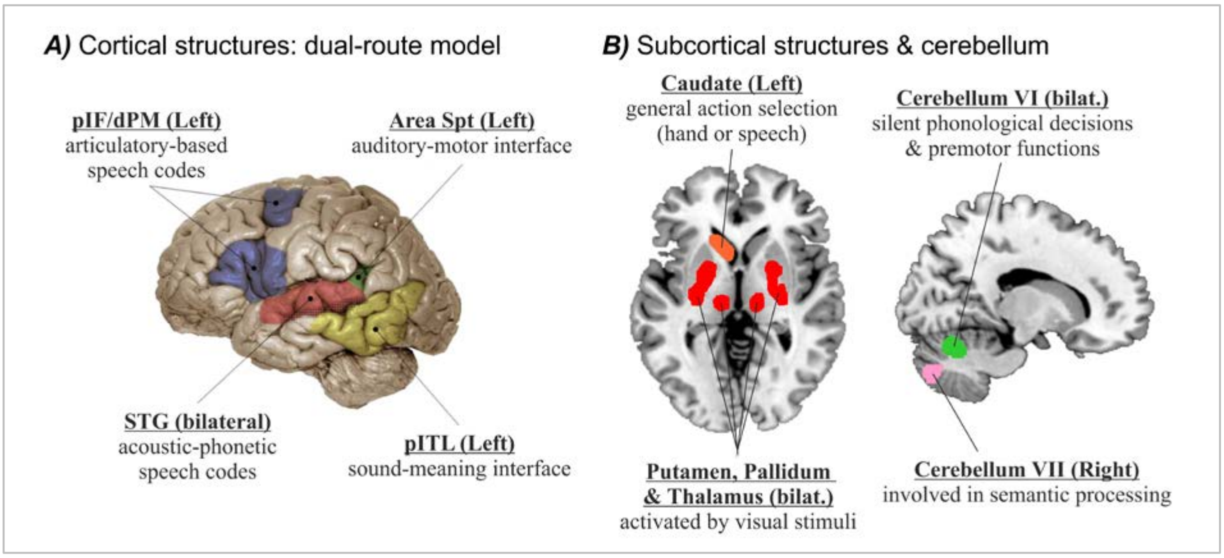


Figure 1.5. Cortical & subcortical GM structures involved in language processing. A) Cortical structures described for the dual-route model: in blue, IFG and dorsal premotor cortex, in charge of the motor planning and articulatory-based functions; in green, parieto-temporal junction, carrying out the auditory-motor integration processes; in red, the superior temporal regions, processing the auditory-phonetic content of the stimuli; in yellow, the inferior temporal areas, involved in mapping the speech sounds with their meanings. [Adapted from Hickock and Poeppel (2004)]. B) Other structures reported to be involved in language processing: subcortical structures such as the basal ganglia, and the cerebellum, specifically parts VI and VIII. [Adapted from Price (2012)].

An interesting aspect of language is prosody, a feature supplying both linguistic (intention, focus, discourse meaning) and non-linguistic (emotional) information (Gandour & Krishnan, 2016; Paulmann, 2016). Prosody comprises many different aspects: accent, stress pattern, prosodic boundaries, intonation and rhythm (Magne et al., 2003). Although studies on prosodic processing are still scarce and its neural substrates are still under debate, it has been proposed that more emotional-related prosody is processed in the right hemisphere. Specifically, Zatorre and colleagues hypothesized that the left cortical auditory areas are better tuned for language and speech processing (Zatorre, Belin & Penhune, 2002), while the right auditory regions would be mostly involved in pitch and tonal-related analysis (Zatorre, Evans, Meyer &

Gjedde, 1992; Zatorre et al., 2002; Zatorre, Chen & Penhune, 2007). This later result has been linked with subsequent findings that interpret the right-hemisphere involvement of auditory regions in prosodic processing (Friederici & Alter, 2004; Magne et al., 2003). Interestingly, a recent study by Sammler, Grosbras, Anwander, Bestelmeyer and Belin (2015) described a dual route for prosody processing on the right hemisphere, analogous to the one described in the left for other characteristics of language. This right lateralized dual-stream model consists in a ventral stream processing time-invariant information given by the prosodic contours ("prosodic objects" that may be linked to a meaning, such as the emotion that prosody can transmit), and a dorsal pathway that may evaluate the temporal information and changes in the prosodic contours (thus, extracting information about how the prosody is produced; Sammler et al., 2015). Curiously, a recent study by Andics and colleagues (2016) has described a similar pattern of verbal-utterances processing in dogs: meaningful words (regardless of their intonation) were processed on the left hemisphere, whereas intonation information was processed exclusively on the right hemisphere. Moreover, the authors described that reward regions of these animals responded most strongly when both lexical and intonation information was coherent (Andics et al., 2016), paralleling language and linguistic emotional processing in humans (Kotz & Paulmann, 2011; Salimpoor et al., 2013).

Regarding the hemispheric distribution of this language network, although classical regions such as Broca's and Wernicke's have been consistently found in the left hemisphere when related to linguistic stimuli, language processing has been related to both hemispheres (Paulmann, 2016). As a matter of fact, right auditory cortex and its related networks have been described as involved in musical functions related to speech like pitch discrimination and perception (Coffey, Herholz, Chepesiuk, Baillet & Zatorre, 2016; Herholz et al., 2015; Johnsrude, Penhune & Zatorre, 2000; Schneider et al., 2002), tonal/melodic pattern processing (Foster & Zatorre, 2010; Patterson, Uppenkamp, Johnsrude & Griffiths, 2002) or tonal working memory (Albouy et al., 2013; Grimault et al., 2014). Importantly, these functions are not exclusive to music and may help to perceive the speech contour or the prosodic content of linguistic streams. These cortical regions would not be able to work in such a coordinated and complex way as language function requires, if they were not in constant communication with each other, connected by important white-matter fibre bundles.

Diffusion weighted MRI (DW-MRI or Diffusion Tensor Imaging/DTI), a neuroimaging technique measuring the motion of water molecules inside a tissue in order to extract information and infer details regarding the underlying microstructure of that tissue (Beaulieu, 2002; Jones, 2008), allows us to both track individual pathways via in-vivo dissections (Catani & Mesulam, 2008) and compare voxel-by-voxel via Tract-Based Spatial Statistics (Smith et al., 2006) the microstructural properties of the white-matter pathways of the brain. Thanks to recent DTI studies, we count nowadays with a quite clear picture of the white-matter fibre tracts included in the dual-stream model.

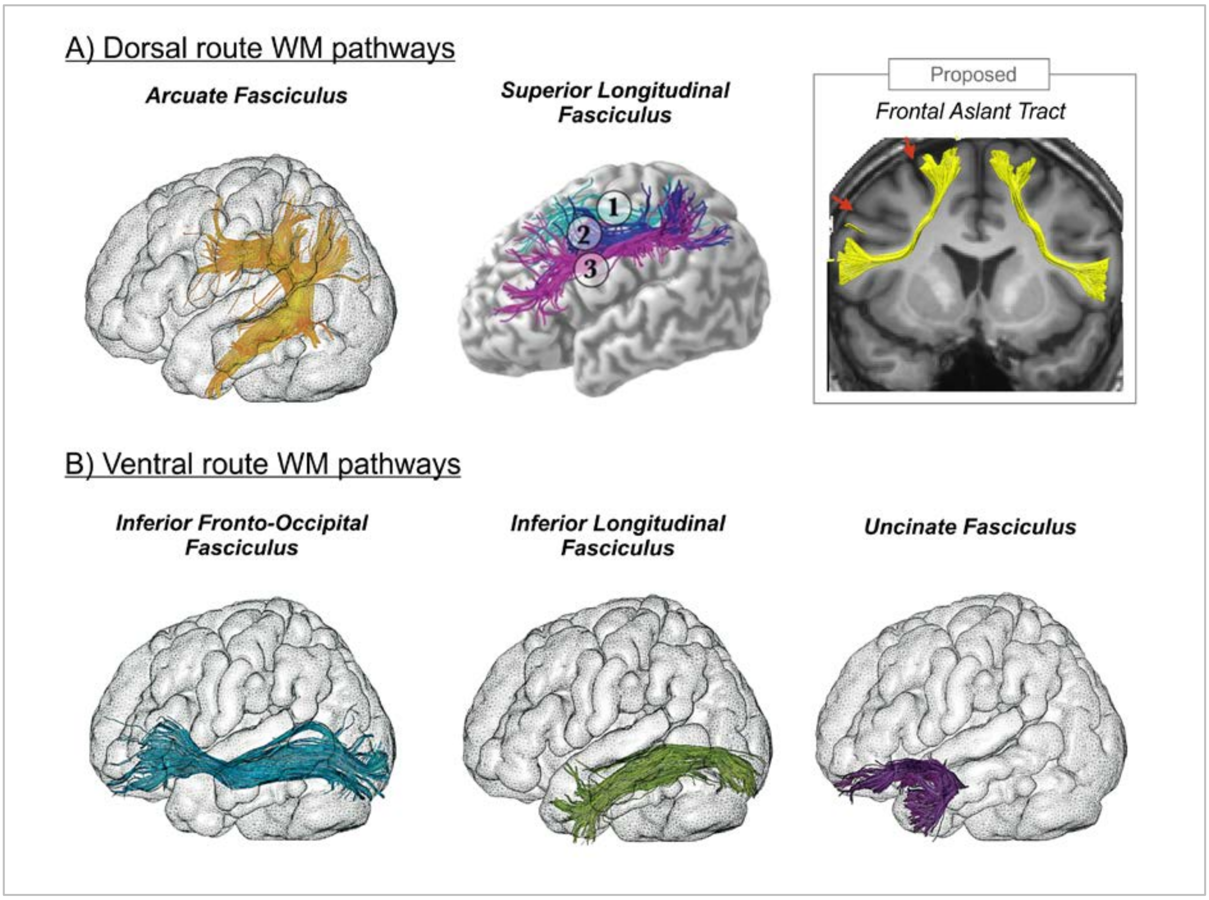


Figure 1.6. White-matter pathways described for the dual-route theory of language processing. A) Dorsal-route includes the arcuate fasciculus [adapted from Catani et al. (2008)] and the superior longitudinal fasciculus (divided in three subsegments) [adapted from Thiebaut de Schotten et al. (2014)]. We also propose that the frontal aslant tract could be part of the dorsal-route due to the areas it connects, involved in motor planning and motor control (supplementary motor areas) as well as language articulation (IFG). [Adapted from Catani et al. (2012)]. B) Ventral-route contains the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus and the uncinated fasciculus. [Adapted from Catani et al., (2008)]. Abbreviations: WM, white-matter.

The dorsal route for language has been identified with the arcuate fasciculus (AF) and the Superior Longitudinal Fasciculus (SLF). It is important to note that, depending on the study, the AF can be also named SLF or include some of the SLF rami (SLF III, mainly; Fernández-Miranda et al., 2015; Wang et al., 2015; see also a view from monkey/human comparisons by Petrides, Tomaiuolo, Yeterian & Pandya, 2012). The AF connects areas beyond the classically described ones (Catani, Jones & ffytche, 2005):

Broca's territory, comprising the inferior frontal gyrus (IFG: BA 44 and BA 45), middle frontal gyrus (BA 46) and the premotor cortex (BA 6); Wernicke's region, including the posterior temporal gyrus (BA 22) and the posterior middle temporal gyrus (BA 21); and Geschwind's territory which includes the supramarginal (BA 40) and the angular (BA39) gyri, both located in the inferior parietal cortex. The SLF, with three subdivisions, connects the superior parietal cortex with the superior frontal cortex (SLF I), the inferior parietal cortex with the IFG (SLF II), and the premotor cortex with the inferior parietal lobe (SLF III). Both SLF II and III have been related to language functions (Friederici, 2015; Rodríguez-Fornells et al., 2009). Furthermore, recent DTI reports have described a white-matter pathway connecting IFG and middle frontal gyrus with supplementary motor regions, named the frontal aslant tract (FAT, Catani et al., 2013; Martino, de Lucas, Ibáñez-Plágaro, Valle-Folgueral & Vázquez-Barquero, 2012). This pathway has been suggested to be involved in language production, verbal fluency, initiation and monitoring of articulation (Sierpowska et al., 2015); perception of communicative intentions (Catani & Bambini, 2014); working memory function in relation to verbal knowledge (Rizio & Diaz, 2016); stuttering, and thus, it could be related to rhythmic perception or learning (Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier & Ben-Shachar, 2016). Due to the cortical areas that connect, it seems to play a role in motor planning during articulation and hence, it could be part of the dorsal-route WM pathways. However, its actual role is still under debate (Sierpowska et al., 2015) and thus, its inclusion in the language processing network will have to wait for more conclusive results.

The ventral route for language processing has been related to several white-matter pathways, all of them connecting the temporal and frontal lobes: the inferior fronto-occipital fasciculus (IFOF: connecting IFG –BA 45 and 47– and orbitofrontal cortex with superior and middle temporal gyri, the inferior parietal lobe and the occipital lobe), the inferior longitudinal fasciculus (ILF: connecting the occipital and temporal lobes, with short fibres connecting visual areas to the amygdala and hippocampus), and the uncinate fasciculus (UF: connecting more anterior parts of the IFG –BA 47–, the orbitofrontal cortex and the frontal operculum with the anterior temporal lobe). Although the function of these three pathways is still under debate, previous reports relate them to different aspects of lexical and semantic processing (Catani & Mesulam, 2008; Friederici, 2015). Figure 1.6 depicts the white-matter pathways reported to be part of the dorsal (Figure 1.6A) and ventral (Figure 1.6B) routes.

1.3.2 Predispositions to phonological processing

Since the language aspect measured in the present dissertation was foreign-language imitation, phonological traits and abilities are a key feature to explore. Adult individuals show an important variability in their aptitude and speed for acquiring a new language (L2), especially for the acquisition of the L2 sound system (phonetic and phonological traits) (Golestani & Pallier, 2007; Hu et al., 2013; Reiterer et al., 2011). The explanations for these individual differences have been related to a variety of causes, from a special genetic background to differences in memory abilities, intelligence, personality factors such as motivation and even empathy (Jilka, 2009; Zatorre, 2013). The view contemplating a set of factors inherent to the speaker and not-modifiable by external influences, is related to the general term of "talent" (Green & Bavelier, 2008). The most prevalent view from phonetically-oriented studies, however, leaves aside the inherent learner characteristics, focusing more on external factors such as age of learning, age of arrival and length of residence in a foreign country, or amount of L1 and L2 use (Jilka, 2009). Moreover, despite a few neurologically-oriented studies regarding talent for language, the study of this field and its neural correlates is not yet broadly established (Jilka, 2009; Reiterer et al., 2011).

A typical distinction in the research field of L2 acquisition has been drawn: there is a talent for grammar and a talent for accent (Schneiderman & Desmarais, 1988). Several studies have shown that, after puberty, the proficient acquisition of the phonetic subsystem (including accent) of the L2 is difficult and rare (Jilka, 2009), although possible (Amunts, Schleicher & Zilles, 2004; Bongaerts, Planken & Schils, 1995). Albeit there is not a clear cut-off point and the field rejects the strict Critical Period Hypothesis (Penfield & Roberts, 1959; but also Lenneberg, 1967), several studies have demonstrated that adults are better at acquiring grammar and syntax, compared to tonal features, phonetics and accent (in which children are usually better) (Flege, 1987). Hensch (2005) has proposed that critical periods serve the establishment of particular functions in primary cortices (such as auditory and motor regions), inhibiting competing functions; however, it is not evident whether the association cortices, which are more directly associated with language, would be equally affected by critical/sensitive periods (Jilka, 2009). The commented studies and theories leave open the amount of contribution that biological and external factors may have in the acquisition of foreign-language phonetics. An especially interesting report was the one by Golestani, Price and Scott (2011) observing both training-derived effects (more information about this type of plasticity phenomena can be found in section 1.4.1) and biological predispositions for language performance and career decisions. These authors explored brain structure of expert phoneticians and found: on the one hand, a positive correlation between the size of left pars opercularis and years of phonetic training; and, on the other hand, a multiple/splitted left transverse gyrus in the auditory cortex, a region thought to be established in utero (Golestani et al., 2011). This latter result implies that differences in the transverse gyri were present long before the phonetic training started and could be behind the career choice of those individuals (Golestani et al., 2011).

Despite the lack of studies in this topic and the complex mix of confounding factors that seem to play a role in the native-like performance of an L2, some major influences in the phonological acquisition and processing of L2 have been drawn. Specially important for the present work are those inherent abilities and non-training related factors of the speaker, such as: (i) innate talent (for new sound perception or phonological processing); (ii) motivation level (interestingly, Ripollés et al., 2016, recently described that activity in reward-related regions is linked with new-word learning); (iii) typological proximity of the L1 compared to the L2 stimuli encountered; (iv) general linguistic experience, such as number of L2 (L3, L4) proficiently spoken; (v) phonological working memory capacities; (vi) handedness (affecting the hemispheric organization of language processing) and sex (with women presenting higher performance than men in semantic and syntactic tasks, Reiterer, 2009) (Bongaerts et al., 1995; Bongaerts, 1999; Bongaerts, Mennen & Slik, 2000; Moyer, 1999).

1.3.3 Language imitation: neural substrates and processing, and relation to singing

As previously mentioned, the linguistic aspect addressed in this dissertation is foreign-language speech imitation, which is an activity encompassing several functions and traits of language processing (from pure perception of individual sounds/phonemes, to speech-contour processing). Imitation tasks rely on the accurate perception of the input stimuli, focusing on prosodic patterns in the case of speech materials coming from the native tongue, as well as on the capacity to correctly reproduce the representation of the model stimuli (Jilka, 2009). However, for imitating a new language, the attentional focus should be centered in perceiving all the sounds and phonotactic structures that differ and are not present in the native (or other known) language(s), adding a higher level of complexity both in the perception part and in the articulation and pronunciation of all the new sounds (Jilka, 2009). There are basically three steeps in which speech imitation can be summarized:

a) *Perception phase*: in this step, all the primary and secondary auditory regions are involved: the 'core' (anterior-medial portion of the Heschl's gyrus, including BA41 and BA42), the belt (the area immediately surrounding the core) and the parabelt (adjacent to the lateral side of the belt, partially including BA21 and BA22) (Pickles, 2012; Schneider et al., 2002). It has been suggested that the left auditory areas extract information from rapid alterations in timing and contour aspects along the auditory stream (Poeppel, 2003; Zatorre et al., 2002). In the specific case of speech, these alterations contain cues about how the speaker is pronouncing the different phonemes (i.e., place of articulation or where in the oral cavity and in which way is the model speaker pronouncing the phonemes) (Idsardi & Monahan, 2016; Poeppel, 2003), which is a crucial information for the listener who tries to imitate these new sounds in the exact way he/she perceives them.

b) Following the perceptive phase in which the imitator centers his/her attention in the articulatory information from the model, speech and voice imitation tasks require the existence of an *Auditory-to-motor mapping process*: the AF might be the most important contributor to this step, since it is connecting auditory regions with articulatory areas (IFG and premotor regions), although the FAT might also be involved in motor-planning aspects of pronunciation. As it has been previously described (Zatorre, Evans, Meyer & Gjedde 1992), the left IFG/BA6, premotor areas and surrounding regions may access to articulatory representations already stored in the system. Then, IFG and premotor cortices may transmit information about the articulatory sequences about to occur (feedforward) into auditory and inferior parietal regions (Rauschecker, 2012). This process allows the repetition of phonological elements (Canevari, Badino, D'Ausilio, Fadiga & Metta, 2013) and possibly other acoustic characteristics as well (such as prosodic pattern, Sammler et al., 2015).

c) In parallel to the articulation of the new sounds, it is necessary to *control the imitation performance and correct for possible mistakes*: parietal regions receive information regarding ongoing pronunciation (feedback) (Rauschecker, 2012), and this information is compared to the auditory templates stored in the posterior STG, which contain information from previous expositions to the unknown language (Warren, Wise & Warren, 2005). This template-matching process may allow the detection of coincidences or differences between the stored phonological templates and the actual pronunciation (Warren et al., 2005), minimizing the articulatory errors (Rauschecker & Scott, 2009), and allowing the correction of possible mistakes by the IFG and premotor areas (which may act as a top-down regulatory mechanism of all the process).

For the description above, we can conclude that a network comprising IFG, premotor, auditory and inferior parietal regions is the one involved in foreign-language imitation. Furthermore, the AF seems the most plausible and crucial white-matter bundle to be involved transmitting the information in this feedforward/feedback loop between perceptive, multisensory integration and articulatory abilities.

Interestingly, an eminently musical task as singing has been reported to share, to a great extent, this “language processing/imitation network”. Schön and colleagues (2010) performed two experiments comparing fMRI activations for language, music and song perception and discovered an overlapping activity for this three types of stimuli in a network encompassing middle and superior temporal gyri and inferior and middle frontal gyri, concluding that activity in those regions cannot be claimed as specific for any of these domains, although some previous reports described distinct network for word (left lateralized) and singing production (right lateralized) (Jeffries, Fritz & Braun, 2003). Based on fMRI and PET studies, a singing-production network has been described, containing: auditory cortices, primary motor cortices, somatosensory cortices, parts of the insula (mainly the anterior part), anterior and middle cingulate cortex, cerebellum, SMA, and parts of the basal ganglia (mainly thalamus, although putamen and pallidum have been reported as well) (Brown, Martinez, Hodges, Fox & Parsons, 2004; Brown, Martinez & Parsons,2006; Jeffries et al., 2003; Kleber, Zeitouni, Friberg & Zatorre, 2013; Perry et al., 1999; Zarate, 2013; Zarate & Zatorre, 2008); some reports also include the nucleus accumbens and the premotor cortex in this network (Brown et al., 2004, 2006; Jeffries et al., 2003; Kleber et al., 2013). Zarate (2013) proposed an interesting and detailed network for neural control of singing, taking into account vocal motor control, somatosensory and auditory feedback aspects, including as well all the nodes for controlling the phonatory muscles (a schematic reproduction of her proposed network can be found in Figure 1.7). An interesting investigation by Kleber and colleagues (2013) tested singing production in singers and non-singers before and after vocal-fold anesthesia. These authors observed this same ‘singing network’ (including primary sensorimotor cortices, secondary somatosensory cortices, premotor and supplementary motor cortices, left BA44, primary auditory cortices, anterior insular cortex, basal ganglia, middle cingulate and the thalamus) in both groups for singing under normal conditions (Kleber et al., 2013). At a functional level, this singing system is closely related to the one explained above for language imitation and speech motor control: sensory feedback through auditory and somatosensory cortex creates a relationship between motor commands and sensory consequences; then, a forward model associated to premotor regions makes predictions and send action information to the effectors through motor areas; feedback is then used to update the received information, making on-line integration of the current production and correcting the forward model in case some errors are detected (Kleber et al., 2013).

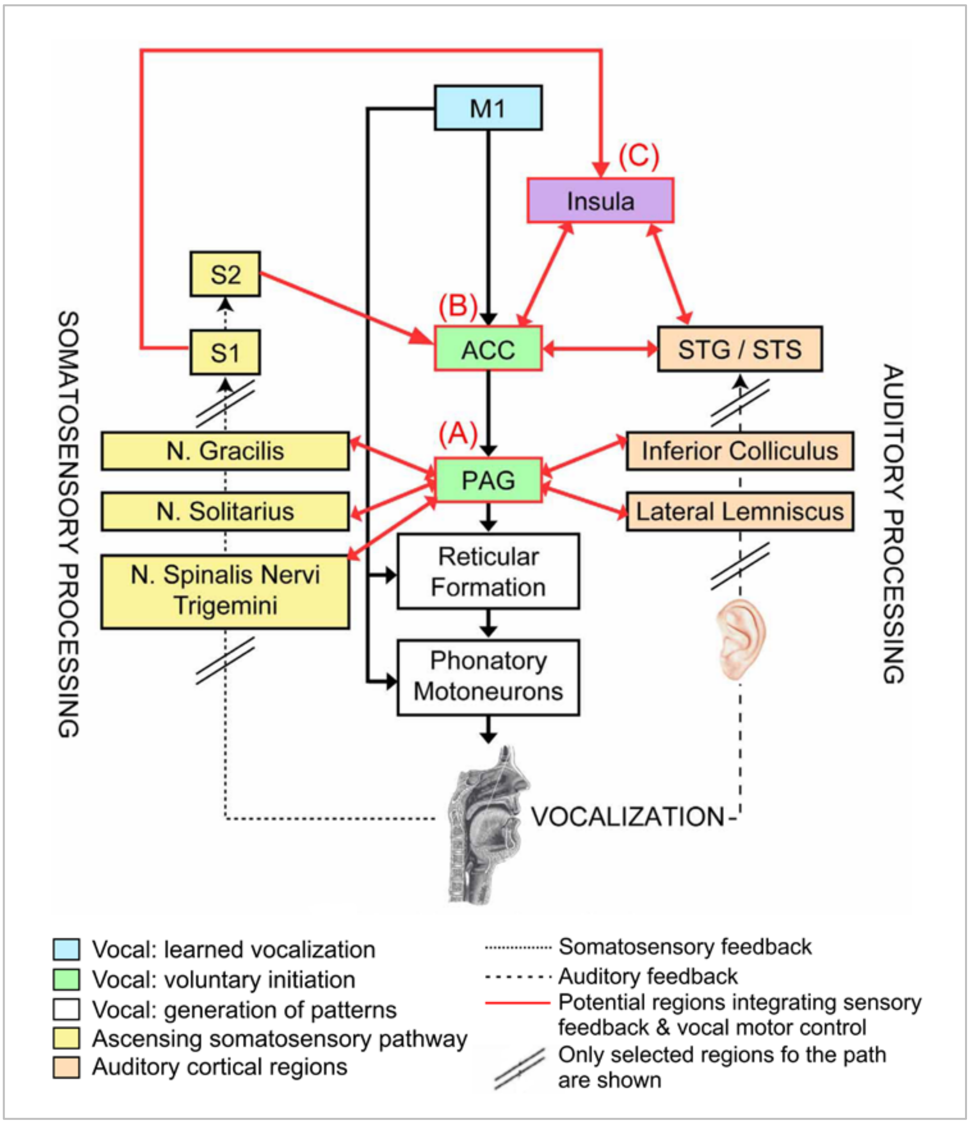


Figure 1.7. Schematic representation of the proposed networks involved in motor control, somatosensory and auditory feedback of singing (which potentially may share some mechanisms and features with foreign-language imitation mechanisms). [Adapted from Zarate, 2013].

Aside from the description of this normal singing network, Kleber and colleagues (2013) discussed a special role in somatosensory feedback for the anterior insular cortex (AIC), a cortical region that has been previously described to be involved in (i) self-awareness of actions (Karnath & Baier, 2010) and mediation of the interactions between attentional networks and self-directed processes (Molnar-Szakacs & Heaton, 2012), (ii) respiration (Ackerman & Riecker, 2010), (iii) coordination of vocal tract activity during singing (Zarate & Zatorre, 2008), as well as (iv) in integration of information coming from the mirror neuron system and the limbic system (which, as a consequence, links AIC with emotional music perception, Molnar-Szakacs & Heaton, 2012). Specifically, Kleber et al. (2013) suggested a key role for the right AIC in experience-dependent modulation of feedback integration during singing, based on the following results: (i) its response to anesthesia was different for singers (in which it was deactivated) and non-singers (in which there was increased activation); (ii) functional connectivity between AIC and bilateral primary motor, somatosensory and auditory cortices was reduced in singers but augmented in non-singers; (iii) activity in right AIC in singers was positively correlated with pitch deviation during singing performance under anesthesia.

We propose that this network could be also used for foreign-language imitation, at least during the first contact with the new language, due to the cues that the listener may try to find in prosodic information and melodic contour of speech.

1.3.4 Music processing

Playing and listening to music are extraordinarily complex, culturally conditioned, but also important natural human abilities (Zatorre et al., 2007). Music processing involves similar functions as the ones described above for language processing: perceptive functions, fine motor control and organization of movements, and an auditory-motor integration that allows information transfer during these two activities (Tillman, 2012; Zatorre et al., 2007). Moreover, syntax and semantics have been described as crucial features to process from musical streams as well (Koelsch, Fritz, Schulze, Alsop & Schlaug, 2005; Patel, 2003; Patel et al., 2008; Tillmann et al., 2000). Musical syntax has been described to activate inferior frontolateral cortices, ventrolateral PMC, and the anterior part of the STG (areas related to sequencing of auditory information, identification of structural patterns and serial prediction), while semantics have been related to activity in posterior temporal regions (Koelsch, 2005). This pattern of activation reveals an important overlap with syntax and semantic processing in language and music (Koelsch, 2005).

Music perception and auditory-motor interactions for music processing have been suggested to involve the same dual-stream network of cortical regions proposed for language (see Figure 1.5A) (Zatorre et al., 2007). Performing a musical piece needs precise control of timing over a considerable window of time in order to follow a hierarchical rhythmic structure, and also requires the musicians to control pitch, to produce the specific musical intervals expected in that piece, which is not as relevant for speech (even in tonal languages information regarding specific intervals between sounds are not as crucial as pitch contours; Zatorre et al., 2007). Moreover, temporal precision and information extracted from the rhythmic structure is essential in order to create music expectations, which allow both the listener and the performer making predictions (musical expectations and predictions have been reported to be a key process in relation to the pleasurable effect that music possesses, Salimpoor, Zald, Zatorre, Dagher & McIntosh, 2015; van den Bosch, Salimpoor & Zatorre, 2013). Even though music production requires some areas that are not included in the model for language processing, the dual-stream model can be adapted to explain the perception of music material. It has been described that the dorsal cortical areas (i.e., parieto-temporal boundary, posterior frontal regions, including IFG/Broca's area, and premotor regions) may track changes in spectral information (frequency distribution of the sounds) over time, perform auditory-motor transformations, and process spatial information (Zatorre et al., 2007). The ventral regions, on the other hand (i.e., the middle and superior temporal cortices, as well as inferior temporal and the anterior temporal pole), are thought to process time-independent characteristics of the sound, which are less related to the motor systems (Zatorre et al., 2007). Melodies (patterns of alternated pitches over time) are known to engage neural populations in both anterior and posterior auditory pathways, with the right-hemisphere being more tuned to process tonal information, as described in previous research (Poeppel 2003; Zatorre et al., 2002, 2007). An alternative cortical organization proposes 4 functional networks: (i) IFG, anterior STG and ventrolateral PMC are in charge of processing the musical structure; (ii) a network encompassing posterior temporal regions (BA 21, BA 22p, and BA37) related to the processing of musical meaning; (iii) supramarginal gyrus and pre-frontal cortex involved in working memory processes related to music stimuli; and (iv) a network comprising orbitofrontal cortex and anterior insula potentially involved in processing the emotional aspects of music (Koelsch et al., 2005a).

On the other hand, ***music performance*** involves at least 3 basic motor control operations: timing, sequencing and spatial organization of movements. *Timing* skills have been related to cortical and subcortical structures: (i) the cerebellum, in charge of movement trajectory, integration of sensory information, and feedforward control or error correction; (ii) basal ganglia, controlling specific motor parameters (i.e.,force) during timed movements, such as finger tapping; and (iii) the SMA and the PMC, helping in the control of timed sequence execution. Production and learning of *motor sequences* (consisting in ordering individual movements or coordinating the subcomponents of multi-joint movements) is thought to involve: (i) the basal ganglia, in great interaction with frontal cortex during learning, and contributing to automatizing well-learned sequences (Poldrack et al., 2005); (ii) SMA and pre-SMA, involved in organizing or chunking complex movement sequences (Bangert et al., 2006); (iii) the cerebellum, integrating individual movements into unified sequences (Baer et al., 2015); and (iv) premotor and prefrontal cortices, involved in motor production of complex sequences and motor predictions (Bangert et al., 2006; Gaser & Schlaug, 2003; Hutchinson, Lee, Gaab & Schlaug, 2003). Finally, another requirement for expert musical performance is *spatial organization* (of the keypresses, for example), which has been reported to involve (i) parietal, (ii) sensory-motor, and (iii) premotor cortices (Zatorre et al., 2007).

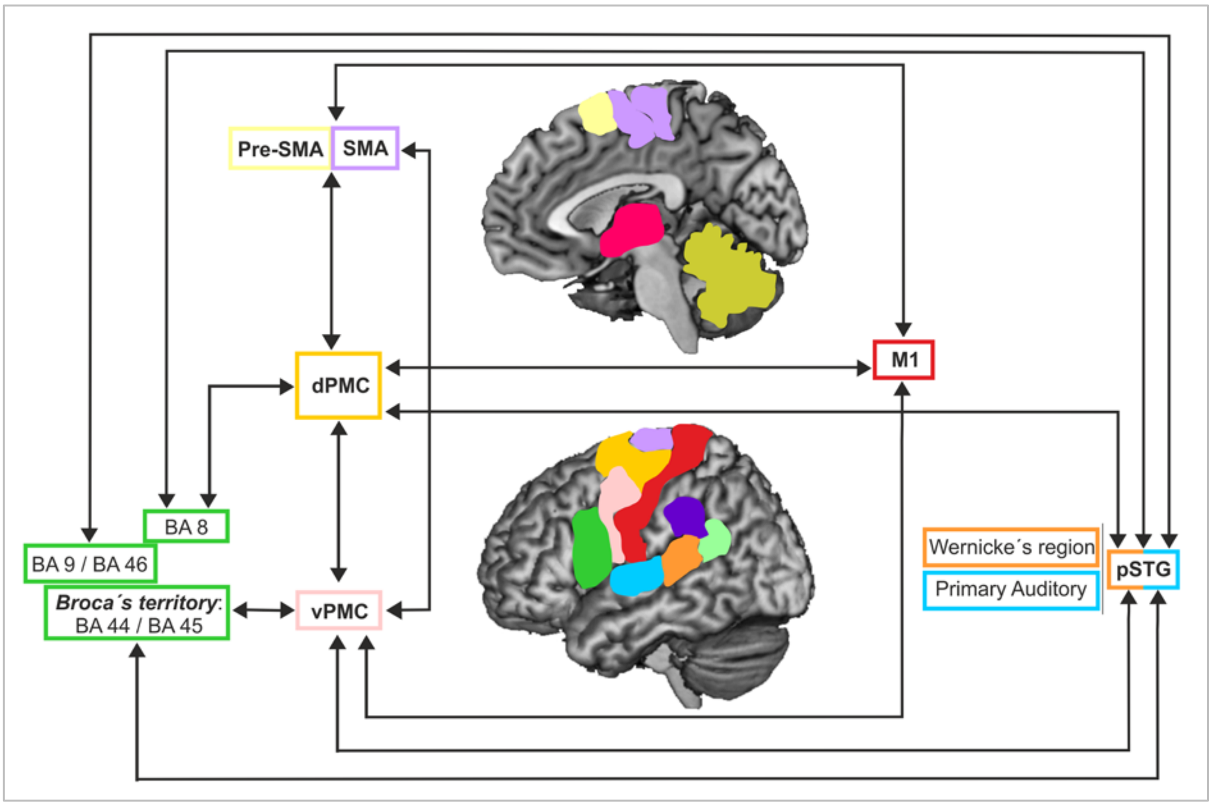


Figure 1.8. Schematic representation of the structures involved in perception, production, feedforward and feedback functions in music processing. Arrow-scheme of the functional connections between cortical regions is an adaptation from Zatorre et al. (2007), and it is based on non-human primates data. Color codes: light yellow: pre-SMA; violet, SMA; magenta, basal ganglia; khaki, cerebellum; red, primary motor cortex (M1); dark yellow, dPMC; light pink, vPMC; purple, supramarginal gyrus; light green, angular gyrus; orange, Wernicke's region; blue, primary auditory cortex; dark green, Broca's territory (BA 44 and 45) and surrounding areas (BA 9, 46 and 8). Abbreviations: SMA, supplementary motor area, dPMC, dorsal premotor cortex; vPMC, ventral premotor cortex; BA, Brodmann's area; pSTG, posterior superior temporal gyrus.

Specifically, the ventral PMC matches properties of a visual object with the appropriate motor gesture; whereas the dorsal PMC may play a role in learning spatial trajectories of movements, has an indirect implication in sensory-motor transformations, is involved in motor planning, prepares and selects movement parameters (such as direction and amplitude) in response to sensory cues, and is also involved in extracting high-order features of the auditory stimulus in order to implement temporally organized actions (Chen, Penhune & Zatorre, 2008a, b; Zatorre et al., 2007). See Figure 1.8 for a schematic depiction of the areas involved in music processing.

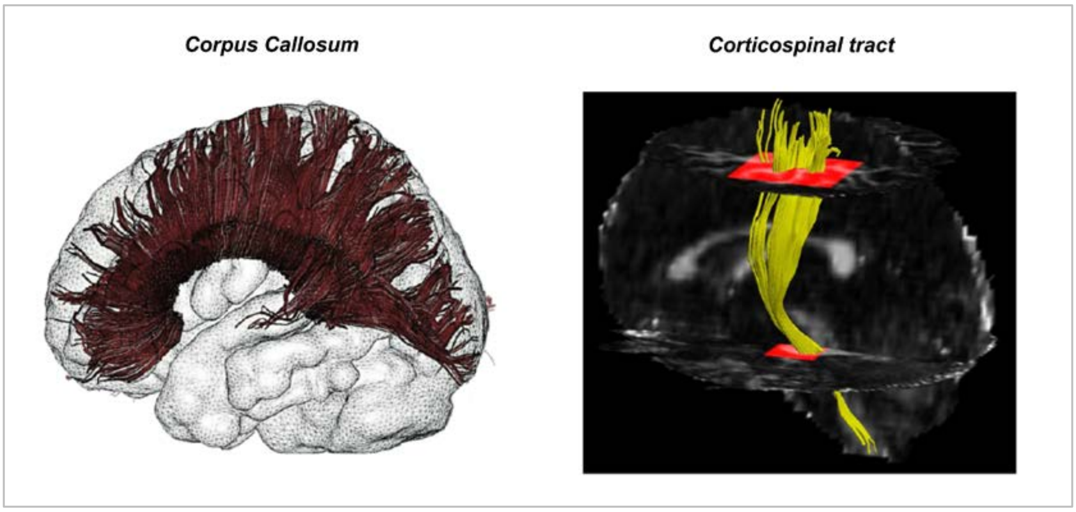


Figure 1.9. WM pathways related to music-processing (aside from the ones shared with language processing, such as the AF or the SLF, or the also already depicted FAT. See all those language-related tracts in **Figure 1.5**). [Adapted from Catani et al., 2008, and Imfeld et al., 2009].

Regarding the auditory-motor interactions needed to perform and "understand" musical stimuli, the posterior auditory-regions, the planum temporale and the temporo-parietal boundary, act as a computational hub, discriminating and categorizing sounds in order to map the correct auditory representations onto motor representations of melodies (Herholz & Zatorre, 2012; Koelsch, 2005; Zatorre et al., 2007). Although the white-matter pathways underlying the dual-stream model for language are thought to play a role equally important for music processing (see Figure 1.6), previous reports correlating these specific dorsal and ventral WM bundles with music abilities or training are still scarce (see Halwani, Loui, Rüber & Schlaug, 2011; Loui, Li, Hohmann & Schlaug, 2011; Oechslin, Imfeld, Loenneker, Meyer & Jäncke, 2010, for music abilities in relation to AF/SLF microstructural properties). Besides, outside the dual-route pathways, two other tracts have been explored in relation to music processing and practice: (i) the corpus callosum, since bimanual coordination is a key activity for most musicians (Begtsson et al., 2005; Schlaug et al., 1995; Steele et al., 2013); and (ii) the corticospinal tract (or the internal capsule, one of the structures that crosses this pathway), as it is the core motor tract, transferring the actions to the limbs during playing (Begtsson et al., 2005; Han et al., 2009; Imfeld, Oechslin, Meyer, Loenneker & Jäncke, 2009; and Luders, Gaser, Jäncke & Schlaug, 2004, for posterior limb of the internal capsule). Furthermore, as it has been described in the previous paragraph, SMA and IFG play an important role both in perception and production of musical material, and thus the frontal aslant tract (FAT) may be expected to be involved in music performance as well. See Figure 1.9 for a depiction of the music-related white-matter pathways, outside the dual-route model.

1.4 Suite for Neural basis of learning

1.4.1 Learning and experience promote brain structural neuroplasticity

Potentially any experience can change the brain, especially if there is a subsequent behavioural change: behavioural alterations require modifications in the neural circuits underlying it (Kolb & Muhammad, 2014). Although time-dependent alterations in brain function over short periods of time have been reported to occur without any formal training, cortical reorganization in response to learning and experience (training-induced neural changes) has been demonstrated (Bayona et al., 2005) for several domains and brain regions, both at structural and functional neural levels (Erickson et al., 2007). As previously mentioned, the ability to learn a new skill is thought to be determined by the capacity of the brain to create new functional connections (Bayona et al., 2005), since these neuroplastic changes will allow the brain to integrate the new learning materials and activities.

The creation of new 'functional connections' described by Bayona and collaborators (2005) encompasses several different plastic mechanisms that Zatorre and colleagues (2012) recently summarized in a very comprehensive way, linking the molecular/cellular alterations with their translation into GM and WM changes observed by using MRI methods. GM changes can be caused by (i) neurogenesis or creation of new neurons that, as previously commented, can be observed in the adult brain in restricted regions; (ii) gliogenesis, that has been reported to be increased in response to learning and experience, affecting both microglia and astrocytes (astrocytes play an important role in synaptic function, homeostasis and blood flow regulation, among other supporting functions); (iii) changes in dendritic organization, as well as creation of new dendritic spines and synapses; (iv) vascular changes, in form of angiogenesis (creation of new vessels) or accompanying neurogenesis; (v) moreover, some signalling molecules, such as BDNF or vascular endothelial growth factor (VEGF), can promote plastic cellular changes, affecting neurons, glial cells or blood vessels (Kolb & Muhammad, 2014;

Zatorre et al., 2012). Several processes can alter WM microstructure, and diffusion imaging measures are sensitive to (i) variations in myelin, both increases/decreases of the myelin sheath in myelinated axons or myelination of unmyelinated axons; (ii) changes in axonal diameter and fiber organization; (iii) axonal sprouting, pruning or re-routing (creation/growing of axons, elimination of axons that are no longer useful or reorganization of existing connections have been reported after physical exercise, creation of new memories and learning); (iv) there is also interactions between neuron and glial cells, among which it is especially interesting the intervention of Nogo-A, a myelin protein that limits structural plasticity, allowing the preservation of already refined systems (Johansen-Berg et al., 2012; Zatorre et al., 2012). A schematic representation of these mechanisms can be seen in Figure 1.10.

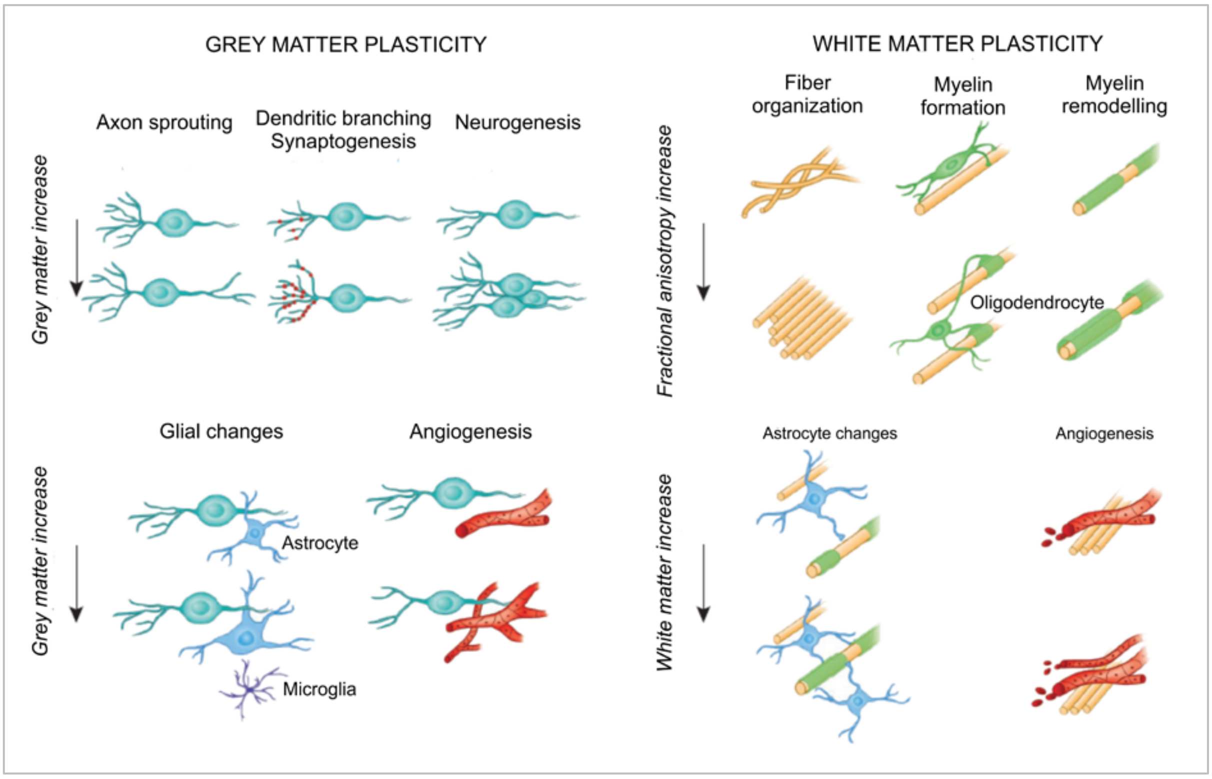


Figure 1.10. Examples of molecular and cellular plasticity mechanisms and how are they translated into MRI measurements (increases in GM, WM and FA). [Adapted from Zatorre et al. (2012)].

Neuroplastic changes at systems level have been reported after short and long training periods. One of the fastest effects regarding neuroplastic phenomena at systems level was reported by Sagi and collaborators (2012), who scanned healthy subjects before and after a 2-hour racing-car video-game training. These authors divided the sample in three groups: (i) a learning group that practiced during the 2-hour training the same track in all the trials (16 times), (ii) a training-control group that was also playing the video-game for the same duration as the learning group but for which the track was different in each trial, and (iii) a second control group that did not perform any task and just waited for the 2h between the 2 scans. They found that only the learning group presented structural plastic changes in their white-matter pathways (specifically, learning-group subjects showed reduced MD in the WM surrounding the hippocampus and parahippocampus, as well as higher FA in the left parahippocampus) (Sagi et al., 2012). Importantly, these authors performed a parallel similar study with rodents, in which the same imaging result was found: reduction of MD in the hippocampus (Sagi et al., 2012). Moreover, Sagi and colleagues (2012) also obtained histological measurements from the rodents, revealing that the learning group had more BDNF, synaptophysin and glial fibrillary acidic protein (markers of neuronal growth, astrocyte activation and synaptic vesicles) in the hippocampus. Reduced MD was interpreted as the consequence of astrocyte swelling, which may change the extracellular-intracellular space ratio, and disruption of BDNF-related LTP processes (Sagi et al., 2012).

In animal research, in addition to the motor-training examples previously commented (Fu & Zuo, 2011; Xu et al., 2009, see section 1.2.3), the effect of diverse stimulation and learning has been extensively studied. For example, Merzenich et al (1984) performed tactile stimulation in owl-monkeys after removal of a single digit and found that, after 2–9 months, neurons from the area representing that digit were now responsive to the adjacent digits. Other classical examples are the experiments using enriched environments, that contain opportunities for several types of cognitive and motor stimulation and training, and that have demonstrated plasticity-related neural alterations and significant brain reorganization (in areas such as the visual cortex, the hippocampus, the cerebellum, the superior colliculus or the sensorimotor cortex, Bayona et al., 2005). Some of the first studies of this kind were performed by Rosenzweig and colleagues (Rosenzweig et al., 1969; Rosenzweig & Benett, 1972), who divided their samples of rodents in two groups that were raised in different contexts: (i) regular cages, and (ii) "enriched-environment" cages (larger cages containing complex elements that facilitates sensory, cognitive and motor stimulation, Fischer, 2016). These authors observed that the rodents raised in enriched environments had a larger cortex, with greater number of cells and connections (Rosenzweig et al., 1969; Rosenzweig & Benett, 1972). Further studies in enriched environments have observed that cognitive exercise in those environments is related to plasticity phenomena such as induction of synaptogenesis (more synapses per neuron), increases in dendritic branching and in cortical tissue (Bayona et al., 2005; Fischer, 2016). These neural modifications are in turn translated into better problem-solving skills when compared to animals living in standard cages (Bayona et al., 2005).

More recent research has demonstrated that physical training such as running in a running wheel for rodents (or in a treadmill in humans) increases the hippocampus neurogenesis in the adult brain (Fischer, 2016). Furthermore, Yang, Pan and Gan (2009) followed dendritic-spine formation using transcranial two-photon microscopy in mice that were trained to run on an accelerated rotarod and on mice that were changed from a normal cage to an enriched-environment cage. These authors found that more than the physical activity (running) per se, it was the motor learning component of the task what was promoting the creation of new spines (after 2 days of training, spines remained higher if mice were training in a different motor task than if they continued in the same task or if they did not perform any task) (Yang, Pan & Gan, 2009). The novel sensory experience obtained in the enriched environment also proved to promote spine creation, that was higher if after two days the animals were changed to another enriched environment (than if they were placed again in regular cages) (Yang, Pan & Gan, 2009). On another experiment using three different versions of the Morris water maze and MRI measurements, Lerch and collaborators (2010) trained mice during 5 days and found that animals trained in a spacial version of the maze (platform was submerged in a fixed location for all trials and the perimeter of the experimental room had several visual landmarks) showed increased GM in the hippocampus, while those mice trained in the spatial-cued version (with a cued platform in a fixed location and the distal visual landmarks visible, allowing spatial memory strategies) had increases of GM in the striatum. In addition, the structure-specific increase in GM was correlated with GAP-43 staining, a marker of neuronal process remodelling (Lerch et al., 2010). A really interesting animal model to study brain plasticity, in close relationship to the topics of this dissertation, is the case of songbirds. De Groof and colleagues (De Groof et al., 2009; De Groof & Van der Linden, 2010) has demonstrated that songbirds that have to change their songs seasonally (such as the *Sturnus vulgaris*), show an extreme plasticity at a whole-brain level. Specifically, white-matter microstructural alterations in relation to these seasonal re-learning of songs have been described in: (i) the song control system, (ii) the optic chiasm, (iii) an interhemispheric connection, (iv) a region analogous to the mammalian secondary auditory cortex, and (v) regions in the ‘social behaviour network’ (DeGroof et al., 2008; De Groof et al., 2009; for a review see De Groof & Van der Linden, 2010).

For human subjects, learning a new skill and sustained practice of a specific activity (such as sports, music or multilingual experience) could be seen as forms of enriched environment accompanied of neural stimulation (Rota & Reiterer, 2009). In humans, numerous examples of brain modifications as a consequence of experience, skill training or expertise can be found (see reviews by Jäncke, 2009; Johansen-Berg, 2010; Zatorre et al., 2012). To put a few almost classical examples, one of the first demonstrations of skill effects in brain structure was the observation of a larger posterior hippocampal volume in expert London taxi drivers, a volumetrical change associated in addition with years of experience (Maguire et al., 1997, 2006). On a longitudinal study, Draganski and collaborators (2004) showed that 3-month practice of juggling changed the GM density in the visual motion area bilaterally, and Driemeyer, Boyke, Gaser, Büchel, & May (2008) observed that the changes were present even after only 7 days practicing. Such fast effects of training were also observed by Taubert and colleagues (2010) after practicing a complex whole-body balancing task: after 2 days of training, changes in GM were present in frontal and parietal cortices, and at the end of the training (duration: 6 weeks) fractional anisotropy in corresponding WM regions was also altered (reduced).

In the learning field, unveiling the mechanisms thanks to which we learn crucial audio-motor functions such as music and language has been an important goal in neuroscience research in the last decades. In order to discover those mechanisms, studying the plasticity phenomena associated to music and language training and the brain regions involved in the process could be extremely useful, and expanding this knowledge is one of the focus of the present work.

1.4.2 Neuroplasticity fostered by linguistic experience

Speaking two languages on a daily basis (i.e., being a bilingual) has proven to have interesting effects in forms of structural and functional brain plasticity, as well as in behavioural performance of linguistic and non-linguistic tasks. Among the first researchers reporting some beneficial effects of bilingualism status, Peal and Lambert (1962) studied French-English bilingual children and observed that they possessed greater mental flexibility and verbal fluency than monolingual peers. Bilingual children are exposed to multiple languages and trained from an early age how to process information in different registers, which has also shown to imply benefits in cognitive control (Bialystok, 2001) and executive functions (measured for example with performance in a Simon task, Bialystok, Craik, Klein & Viswanathan, 2004; Bialystok et al., 2005; Martin & Bialystok, 2003; Morales, Calvo & Bialystok, 2013; see review by Hervais-Adelman, Moser-Mercer & Golestani, 2011), attentional capacities (Rota & Reiterer, 2009), working memory and visuospatial abilities (Morales et al., 2013), as well as in general intelligence (Sundman, 1994, as cited in Rota & Reiterer, 2009). Benefits to executive control have been also recently reported for individuals speaking two closely related dialects of the same language (Antoniou, Grohman, Kambanaros & Katsos, 2016), evidencing that advantages form language training do not require the acquisition of different and unrelated linguistic systems. The suppression of interference needed for bilinguals to use the appropriate language in each situation, seem to rely on the anterior cingulate cortex, the left prefrontal cortex and the dorsolateral prefrontal cortex (Kondo et al., 2004 a,b), areas that are expected to present plastic adaptations due to extensive bilingual practice/experience (Rota & Reiterer, 2009). As a matter of fact, in addition to the left temporal and the superior and inferior frontal areas, the cingulate cortex has been reported to show a characteristic activation in bilinguals when related to executive functioning (Bialystok et al., 2005; Bialystok, Craik & Freedman, 2007). On another study, Garbin and colleagues (2010) found a different pattern of activation in bilinguals compared to monolinguals during a non-verbal switching task, with bilinguals showing a reduced switching cost and a specific activation in the left IFG and the left striatum, regions thought to underlie language control. In more linguistic-related parameters, bilinguals seem to possess more GM volume in Heschl's gyri, a crucial part of the auditory cortex (Ressel et al., 2012), and increased density of grey matter in the left inferior parietal cortex in relation to higher fluency levels (and younger age of acquisition) (Mechelli et al., 2004) when compared to monolinguals.

Among bilingual or multilingual individuals, phoneticians or simultaneous interpreters are a special type of experts, practicing to a greater extent their executive function abilities (Hervais-Adelman et al., 2011; Hervais-Adelman, Moser-Mercer & Golestani, 2015; Hervais-Adelman, Moser-Mercer, Michel & Golestani, 2015). Hervais-Adelman and collaborators (2015a) performed a longitudinal study, scanning subjects before and after long-term (15 months), intensive training in simultaneous interpretation, and found that activation in the right caudate nucleus during the in-scan simultaneous interpretation task was reduced after training, indicating a higher degree of automatization of the task. This same group (Hervais-Adelman et al., 2015b) also found activations in regions known to be involved in speech perception and production (left IFG, pre-SMA, ACC, left anterior insular cortex and SMA) as well as in the caudate (also thought to be implicated in cognitive control) during a simultaneous interpretation task in comparison to a simultaneous repetition task.

Aside from long-term effects of language training and bilingualism status, language learning has been related to plastic changes in brain structure and function after short-term practice. For example, Golestani and Zatorre (2004) observed functional changes in the language network after 2 weeks of training non-native sounds discrimination abilities (see Figure 1.11). Using an associative learning paradigm during an fMRI session, Breitenstein and colleagues (Breitenstein et al., 2005) found that modulations of activity within the left hippocampus and the left fusiform gyrus were associated to increasing vocabulary proficiency. As another example, Stein and collaborators (Stein et al., 2012) examined the brain structure of native English subjects before and after a 5-month German-language training, and found a correlation between increases in grey matter density in the left IFG and the left anterior temporal lobe and subjects' German proficiency.

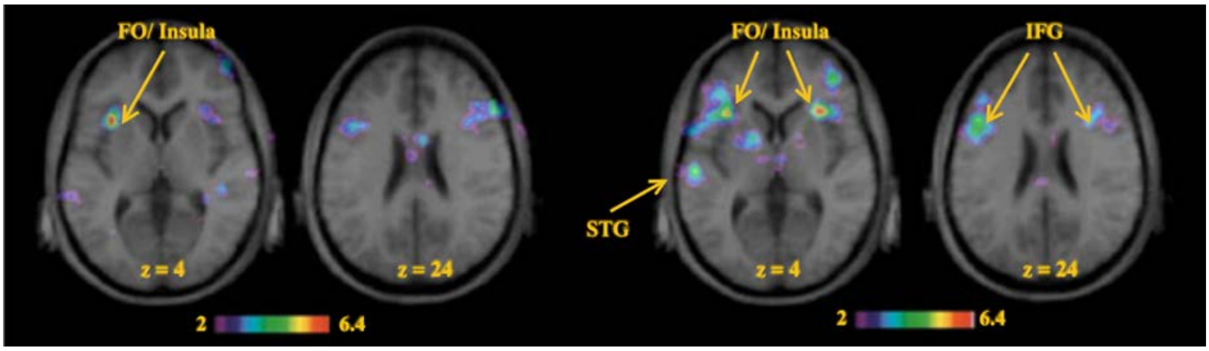


Figure 1.11. Example of structural plasticity after language learning. The pair of axial slices on the left show the activation pattern before training while listening to non-native contrasts; the couple of axial slices on the right show the change in activity during non-native contrast exposure after 2 weeks of training, revealing a pattern more similar to the one observed while listening to native stimuli. [Adapted from Golestani & Zatorre (2004)].

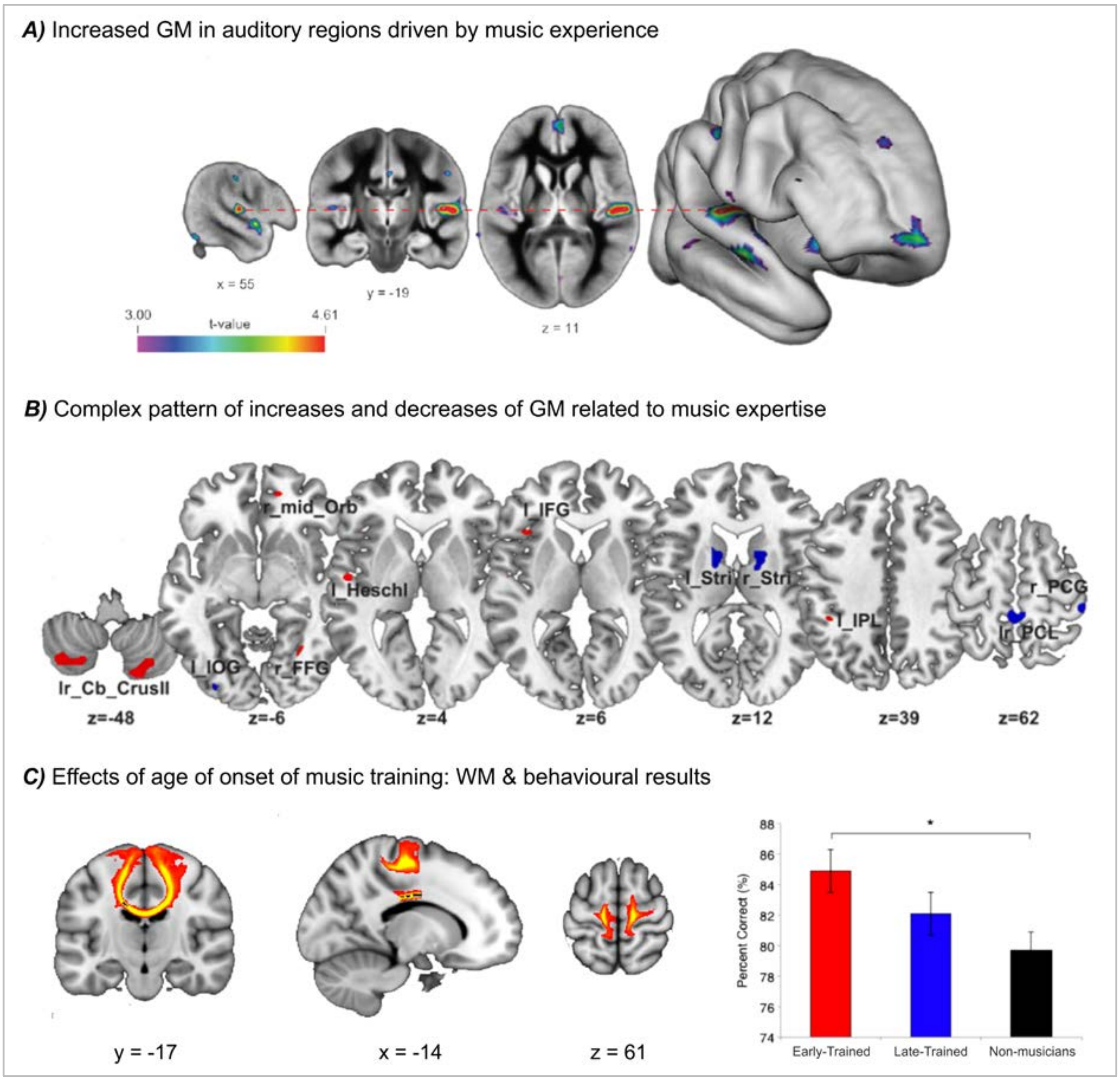
From the examples given above, we can infer that some areas are sensitive to language training-induced modifications (IFG, striatum). However, some brain differences found in bilinguals or in cross-sectional imaging studies could be the result of genetic predispositions that enhance language abilities (Reiterer, 2009).

1.4.3 Neuroplasticity triggered by musical experience

Music is a complex and multimodal training, that involves practicing fine motor skills, limb and bimanual coordination, auditory and somatosensory perception, audio-motor integration, and several cognitive functions such as attention, executive functions and memory, all under a great amount of emotional content that transforms musical practice in an enjoyable and motivational experience (Schmithorst & Wilke, 2002; Zatorre et al., 2007; for a review see Koelsch, 2010; Pantev & Herholz, 2011).

Several investigations have been focused in the comparison between musicians and individuals without musical background (non-musicians), in order to study the neural substrates of long-term music training. These investigations have consistently reported structural and functional plastic changes associated with playing an instrument (such as the examples explained in section 1.3.4) in motor control regions (i.e., primary motor, supplementary motor regions, premotor cortex: Bailey, Zatorre & Penhune, 2014; Bangert et al., 2006; Bozkurt et al., 2016; Chen et al., 2008a,b; Gaser & Schlaug, 2003; Bermudez, Lerch, Evans & Zatorre, 2009), areas related to automatization of movement and motor learning (i.e., basal ganglia, cerebellum: Baer et al., 2015; Gaser & Schlaug, 2003; Granert, Peller, Jabusch, Altenmüller & Siebner, 2011; Hutchinson et al., 2003; James et al., 2014; Poldrack et al., 2005), proprioceptive areas (i.e., somatosensory cortex: Bermudez et al., 2009; Gaser & Schlaug, 2003; James et al., 2014), auditory processing regions (i.e., primary and secondary auditory cortex, Heschl's gyrus: Bermudez et al., 2009; Chen, Rae & Watkins, 2012; Gaser & Schlaug, 2003; Herholz et al., 2015; Luders et al., 2004; Schneider et al., 2002, 2005), limbic regions (i.e., hippocampus, amygdala, cingulum: Bangert et al., 2006; Hutchinson et al., 2003; Koelsch, 2014; Salimpoor et al., 2013), and even some classical language-related areas (i.e., Broca's territory: Bangert et al., 2006; Bermudez et al., 2009). Moreover, the white matter bundles connecting these regions (such as the corticospinal tract, Engel et al., 2014; Imfeld et al., 2009; Schmithorst & Wilke, 2002; or the arcuate fasciculus, Halwani et al., 2011; Loui et al., 2011) and the corpus callosum, the tract controlling interhemispheric transit of information and thus helping bimanual coordination (Bengtsson et al., 2005; Schlaug et al., 1995; Steele et al., 2013), have been also observed to suffer plastic alterations after sustained musical practice. Most of the times, the results have shown that musicianship is associated with increased volume or density of grey matter and with an enhanced microstructural organization of white-matter. However, recent investigations have started to find more complex patterns in which some areas present an increase in GM, while others seem to have undergone a shrinkage of GM (James et al., 2014). See Figure 1.12 for several examples of previous reports regarding neuroplastic effects induced by music experience.

An important consideration in previous studies has been the effect of the age of start of musical training, inspired by the concepts related to the sensitive period theories (see section 1.2.4). The current view, supported by findings in different populations and explored by different laboratories (Amunts et al., 1997; Baer et al., 2015; Bailey et al., 2014; Bengtsson et al., 2005; Pantev et al., 1998; Schlaug et al., 1995; Steele et al., 2013), is that the central nervous system possesses its maximum malleability during early phases of development and maturation periods (childhood and adolescence), and that it is during these stages that the commencement of music training has its maximum benefit and effect on the brain. Thus, the earlier the start of the training, the greater would be the neuroplastic changes associated with the training, with a frequent delimitation of 'early' as any age before 7 years. Check Table 1 in the first experimental chapter (Chapter Chapter 3) to know more details about some of the previous studies regarding musicians vs. non-musicians and age-of-onset effects in musicians.



A) Increased GM in auditory regions driven by music experience

B) Complex pattern of increases and decreases of GM related to music expertise

C) Effects of age of onset of music training: WM & behavioural results

Figure 1.12. Several examples of brain plasticity reported after long-term music training. A) Increased GM has been reported in right auditory regions [Adapted from Bermudez et al. (2009)]. B) Recent studies showed a complex pattern of increases and decreased GM in different regions of the brain in relation to musical expertise [Adapted from James et al. (2014)]. C) Moreover, most of the studies investigating effects of age-of-onset of musical training, show an enhanced brain structure (GM or WM) and a better performance related to an early start of music practice. In this case, corpus callosum showed more FA in the early-trained musicians compared to both late-trained and non-musicians [Adapted from Steele et al. (2013)]; the graph on the right of this panel shows the percentage of correct response in a rhythm synchronization task: early-trained outperformed the other two groups [Adapted from Bailey et al. (2014)].

Furthermore, there are also several reports investigating not the long-term effects of musical training, but the plasticity phenomena associated to the initiation of music training. Those are studies in which non-musician individuals have undergone a musical training and brain function has been tested before and after the training period. As an example, Pascual-Leone (2001) trained non-musicians in playing a 5-finger sequence on a keyboard for 5 consecutive days and observed that, as subject's performance improved, TMS activation of the finger's flexor and extensor muscles decreased, while the size of the cortical representation for both muscle groups increased significantly. In another investigation, Stewart and colleagues (2003) trained musically naïve participants to play the piano and read musical notation for 15 weeks. These authors found that when subjects played melodies from musical notation after training, activation was observed in the superior parietal cortex bilaterally, which they interpret as a sign of sensorimotor translation of the spatial code (music notation) into the corresponding motor responses (keypresses) (Stewart et al., 2003). Results of these examples can be seen in Figure 1.13.

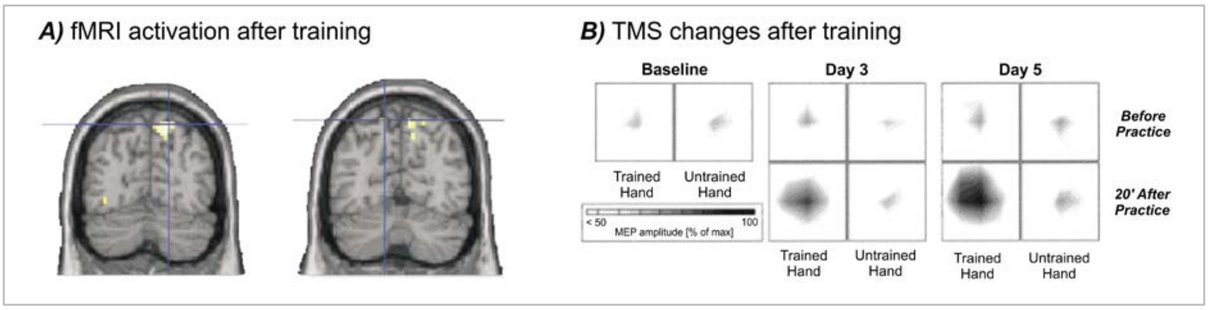


Figure 1.13. Examples of the effect of short-term musical training in non-musicians. A) Bilateral superior parietal areas were seen as active when participants played melodies while reading from the score after training. [Adapted from Stewart et al. (2003)]. B) TMS activation of the finger flexor and extensor muscles is decreased after a 5-days training of playing a sequence in the keyboard. [Adapted from Pascual-Leone (2001)].

Behaviourally, these plasticity effects on brain structure and functional patterns of activation are translated into benefits for music- and non-music-related activities (Besson, Chobert & Marie, 2011; Kraus & Chandrasekaran, 2010; Moreno & Bidelman, 2014; Patel, 2014). These transfer benefits triggered by long-term musical training have been reported to enhance several neural functions such as: (i) auditory analysis, encoding of complex sounds and auditory discrimination (Bidelman & Krishan, 2010; Bidelman, Gandour & Krishnan, 2011; Chartrand & Belin, 2006; Parbery-Clark, Skoe & Kraus, 2009; Zendel & Alain, 2009); (ii) speech perception and verbal intelligence (Anvari, Trainor, Woodside & Levy, 2002; Degé & Schwarzer, 2011; Degé, Kubicek & Schwarzer, 2011; Moreno et al., 2011); (iii) linguistic prosody abilities (Bidelman et al., 2011; Moreno et al., 2009; Wong et al., 2007); (iv) attentional processing, general intelligence and executive functions/working memory (Besson et al., 2011; Kraus & Chandrasekaran, 2010; Moreno et al., 2011; Pallesen et al., 2010; Schellenberg, 2004); as well as (v) motor function and synchronization ability (Baer et al., 2015; Bailey & Penhune, 2012; Chen et al., 2008a). In addition, previous reports conclude, overall, that the enhancement in these brain functions is greater in those musicians who started their training earlier in life (before age 7, generally) (Begtsson et al., 2005; Schlaug et al., 1995; Steele et al., 2013; for a review see Penhune, 2011). To summarize, musical practice has proven to have a deep impact on brain structure and function, especially during childhood and adolescence. In the context of brain predispositions we should keep in mind that, while music training boosts neuroplastic alterations that in turn enhance brain function, this enhancement of neural structure and functional brain networks may also promote music performance and learning (Pascual-Leone, 2001), as well as the motivation to continue practicing music.

However, in contrast to these benefits induced by musical practice and instantiated in the brain via neuroplastic mechanisms, there are also some cases in which neuroplasticity mediates maladaptive processes, associated to unwanted consequences (such as pain or motor problems). Examples of this maladaptive plasticity can be found both in specific disorders and after sustained practice (Altenmüller, Baur, Hofmann, Lim, & Jabusch, 2012; Aránguiz, Chana-Cuevas, Alburquerque & Curinao, 2015; Floor, 2003; Furuya & Hanakawa, 2016; Ramachandran, McGeoch & Williams, 2007). An example related to the topic of this dissertation is musician’s cramp or focal task-specific dystonia. Etiology of musicians’ focal dystonia is complex and multifaceted, with involvement of genetic predispositions (familiar association, male predilection and co-occurrence of anxiety and obsessive-compulsive traits pointing to this "nature" involvement), but also environmental factors such as over-practice of the same motor actions, high-requirements during training, musical instrument characteristics (woodwind instrumentalist more affected than string players or percussionists, for example), and extra-professional burdens (depending whether it is manifested in the dominant hand or in the contralateral one, for example) (Altenmüller et al., 2012; Frucht, 2014; Furuya & Hanakawa, 2016). Moreover, it not only affects the hand, but also the laryngeal or oro-facial muscles, which are behind singers or bouchure dystonia in woodwind instrumentalists (Altenmüller et al., 2012; Halstead, McBroom & Bonilha, 2015). Although it is usually difficult to treat, some new therapies are being tried in order to re-conduct the motoric and sensory organization back to normal, using (paradoxically?) plasticity mechanisms (Flor, 2003; Furuya & Hanakawa, 2016; van Vugt, Boullet, Jabusch & Altenmüller, 2014).

1.5 *Aria* for the DTI-correlational approach

At this point, and before closing the introduction, I would like to include some notes regarding the main methodological approach and analysis performed throughout this dissertation, as well as a few examples of previous investigations that have inspired us to plan our experimental designs and analyses. In order to study predispositions and neuroplasticity phenomena related to music and language skills, as well as how are they represented and instantiated in the structure of the brain, we decided to use structural MRI data (both T1-weigthed data, for GM analyses, and Diffusion-weighted images, for studying WM). As commented earlier in this introduction, we acknowledge the fact that, deciphering the biological meaning of MRI results, interpreting the translation of morphological measurements into cellular/molecular mechanisms, is still challenging (Johansen-Berg et al., 2012; Kanai & Rees, 2011). Even the link between structural and functional findings across different MRI techniques seems complicated and not so clear-cut, although a connection between brain function and structure is expected (Zatorre et al., 2012).

Among the three experiments conforming the present dissertation, one (Study I) is centred in the study of GM differences between musicians and non-musicians measured via Voxel-Based Morphometry of T1-weighted images, a method that compares, voxel by voxel, the possible differences (between groups or in relation to a behavioural variable) in the values assigned in each voxel across the brain GM regions (Ashburner, 2010). By contrast, the other two experiments are focused on studying WM predispositions for music and linguistic abilities using tractography of selected WM pathways. Specifically, Study II used a deterministic-manual tractography (Catani et al., 2005; López-Barroso et al., 2013) and an automatic tractograhy method based on a combined approach between deterministic and probabilistic types of analyses (Yeatmann et al., 2012) in order to dissect the arcuate fasciculus. In Study III, I manually dissected both the arcuate fasciculus and the corticospinal tract using deterministic tractography.

Once the first level of the voxel-based morphometry and the DTI dissections were performed, for the second-level (statistical comparison of interest) we have used simple Pearson's correlations between the MRI measurements (such as GM volume or density, or FA/volumetric values from the WM tracts dissected manually or automatically) and the behavioural variables of interest (such as age of start of musical training, or performance in a speech-imitation or a rhythm synchronization task). This correlational approach was motivated by a large number of previous MRI studies that have shown how individual differences in several basic and higher cognitive functions (i.e., perception, motor control, consciousness or the ability to introspect) can be predicted from the local structure of GM and WM by using voxel-based morphometry, or DTI voxel-wise or tractography methods (Kanai & Rees, 2011).

For example, Tuch et al. (2005) found that individual differences in choice reaction time (the time needed to indicate a choice, usually by pressing a button) correlated with FA values in the optic radiation. In a more complex motor-task, Johansen-Berg, Della-Maggiore, Behrens, Smith & Paus (2007) found that variability across individuals regarding their skill in a bimanual coordination task were reflected in the differences in the integrity of the corpus callosum, specifically in the region that connects with supplementary motor areas. In perception, it has been reported that the size of the surface area of the primary visual cortex determines the inter-individual variability in visual acuity (Duncan & Boynton, 2003).

In more higher-cognitive abilities, Fuentemilla and colleagues (2009) found that greater FA in the ILF was related to higher indices of true-memories retrieval, while greater FA in the SLF was related to an increased susceptibility to false memories retrieval, evidencing that different WM bundles accounts for different individual performance in memory tasks. Another example focused on a completely different function showed that metacognitive ability (the capacity to accurately link insight/confidence to objective performance in a perceptual decision-making task) was reflected in the GM volume of the rostral prefrontal cortex and precuneus (Fleming, Weil, Nagy, Dolan & Rees, 2010), and subsequent studies in this topic have continued to show the link between structural properties of the lateral prefrontal cortex and the metacognitive ability (Fleming & Dolan, 2012). In an interesting investigation regarding language segmentation and rule learning, López-Barroso and collaborators (2011) recruited their participants' dorsal language route with a repetition task, while they were presented with a stream of non-words that they have to learn to segment (blocking in this way the dorsal route for subvocal rehearsal, that could have helped in the rule-learning task). These authors found that when rehearsal was blocked (dorsal route was focused on repetitions of meaningless utterances), performance in the rule-learning task was correlated with individual differences in WM microstructure of the left ventral pathway connecting frontal and temporal language-related areas via the extreme/external capsule (López-Barroso et al., 2011).

The examples given throughout this introduction regarding previous investigations linking behavioural measurements and learning performance in diverse tasks with brain structure by using MRI methods, for studying both plasticity mechanisms and predispositions, give us confidence regarding the validity of applying these correlational analyses to the current work.

1.6 *Last refrain*: Final introductory remarks

As a summary, there are general predispositions all human beings have as members of the species, as it can be the predisposition to learn the language of our community or the brain wiring ready to process musical stimuli from infancy (Fitch, 2010; Perani et al., 2010). Then, the genetical background inherited from our parents determines our phenotype and innate skills and, in addition, it can also predispose individuals to seek the environments and activities that match those skills. But environmental influence has also an important role, since neuroplastic phenomena has been demonstrated after experience and learning (and also after brain injury or an excess of practice), and social interaction may also reinforce the maturational pathway and environmental choices we make during normal development (evocative genetic-environmental interactions as explained by Scarr & McCartney 1983). Following this last idea, social interaction is a crucial aspect both in music and language training, as seen in "real life" experiences but also as has been proven by second language learning paradigms and rehabilitative approaches (in autism, for example) (Molnar-Szakacs & Heaton, 2012; Overy, 2012; Verga & Kotz, 2013).

Alterations in our brain structure would be carried out via neuroplasticity phenomena, which may or may not be mediated by epigenetic processes (inherited altered ways of reading the genetic material without altering the DNA sequence). Moreover, as Zatorre and colleagues explained (2012), behaviour is controlled and expressed by the brain, but may in turn alter the brain functioning and anatomy, modifying and adapting the brain structure in parallel to the current training or environmental demands (Pascual-Leone, 2001). Check Figure 1.14 for a schematic view of the ideas explained here.

The focus of this dissertation is studying the anatomical substrates behind language and musical predispositions in healthy subjects, as well as the neuroplastic effects related to long-term and age-of-onset of musical practice. Musical and linguistic processing are tightly intertwined in the human brain and their defining functions overlap to a great extent in several neural regions (Patel, 2003; Schön et al., 2010; Tillmann, 2012). Both music and language need chunking or segmentation of long streams into individual units (Tillmann, 2012), contain rhythmic and melodic components (Tillmann, 2012; Zatorre et al., 2007), involve a defined structure and underlying rules that can be extracted by mere exposition (i.e., syntax, Patel, 2003; Patel et al., 2008; Tillmann et al., 2000), possess an associated meaning (i.e., semantics, Koelsch et al., 2005a; Patel, 2003), as well as an emotional content with important contributions to the overall message (Paulmann, 2016; Salimpoor et al., 2013).

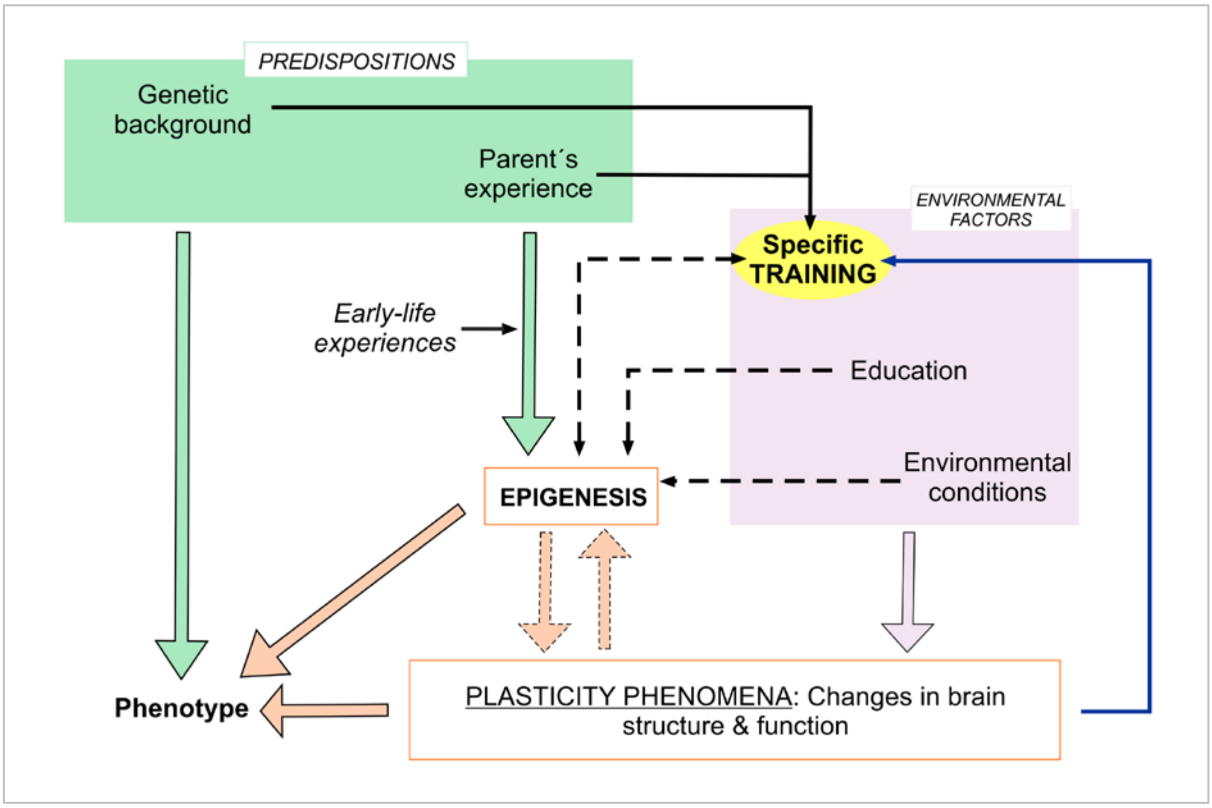
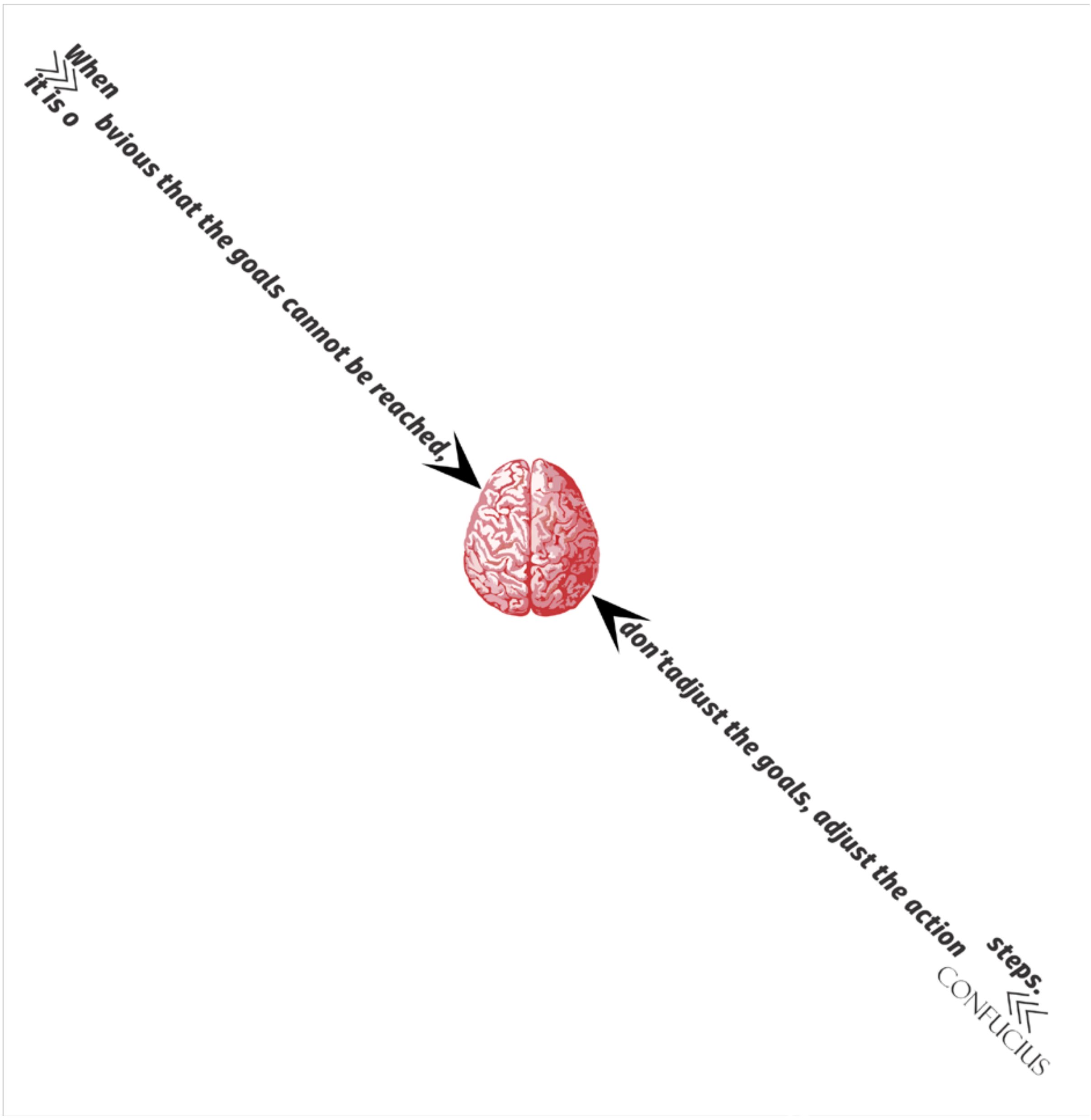


Figure 1.14. Scheme of Nature and Nurture factors determining brain structure. Human phenotype is determined by a combination of genetic and epigenetical predispositions (green box) inherited from our parents and that may be modified throughout our lifetime due to environmental factors (violet box) via plasticity phenomena (in which epigenetic processes may or may not be involved). As it has been commented in the main text, while music/language training promotes neuroplastic changes that enhance several underlying brain functions, this enhancement in brain structure, function and behaviour might also improve music performance and learning (dark blue arrow).

Both music and language involve perception of complex auditory streams; motor reproduction and motor planning for executing verbal utterances, singing or playing an instrument; and a feedback-feedforward loop in charge of on-line integration of verbal/musical production, comparison with previously stored templates, and potential correction when errors are detected (Kleber et al., 2013; Rauschecker & Scott, 2009; Rauschecker, 2012; Warren et al., 2005; Zarate, 2013; Zatorre et al., 2007). These functions are shared to a high extent in both domains and, anatomically, are mainly represented in superior and medial temporal regions, inferior and medial frontal areas, inferior parietal areas and subcortical structures such as basal ganglia, hippocampus and the cerebellum, as well as the white matter bundles connecting them.

Chapter 2 - Research aims



By using structural MRI methods and behavioural tasks, this thesis aims to enlarge our knowledge about the anatomical neural correlates of language and music learning and abilities. In addition, it also pretends to expand our current knowledge regarding the brain-plasticity processes and structural changes related to sustained musical practice and exposure. This dissertation contains three experiments which, although independent of each other, share a common focus on brain anatomy related to processing and learning of auditory-motor functions.

All the data exposed in this dissertation is completely new and has not been included in any other previous dissertation. However, two of the three studies I am going to present have been recently published as original articles in different journals (Study I in *Neuroimage*, Study II in *Cerebral Cortex*).

2.1 Study I: Long-term neuroplastic effects in professional pianists

In the first experiment, we were interested in studying the effects of sustained and professional-level musical training on the cortical and subcortical grey matter structures of the brain. Specifically, we wanted to examine brain structural differences between a homogeneous group of selected musicians (i.e., high-level professional pianists) and a control group of non-musicians. Moreover, we were also interested in investigating the effect of the age of onset of musical training on brain anatomy and its potential relationship with piano performance.

To do so, we obtained T1-weigthed images from a group of non-musicians and a group of expert pianists, who reported their age of start of musical training as well as their amount of hours of current and past piano practice. Furthermore, a behavioural scale playing task performed with both hands independently was also completed by the pianists. We used Voxel-Based Morphometry (Ashburner & Friston, 2000), applying a two-sample t-test, as well as simple correlation (Pearson's) analyses with age-of-onset of music training and performance in the scale playing task.

From the best of our knowledge, this is the first time that effects of musical training depending on the age of onset are addressed in such a homogeneous cohort of expert pianists, taking into account both age of start and amount of practice. Based on previous literature, grey-matter differences in areas related to motor, auditory and emotional processing were expected between the pianists and the non-musicians, and a superior scale-playing performance as well as greater plasticity effects in grey-matter structure related to piano performance were expected in the early-trained group compared to the late-onset pianists.

2.2 Study II: White-matter structural correclates of foreign-language imitation

The second study wanted to shed more light on our knowledge regarding the individual differences in foreign-language reproduction abilities and its white-matter substrates. We were interested in investigating whether the microstructural organization of a language-related tract such as the arcuate fasciculus could predict the performance in a foreign-language imitation task. Moreover, we tested two different tractographic approaches (i.e., a manual and an automatic one) in the detection of white-matter contributions to individual differences in this language task in order to corroborate our results and overcome possible limitations of using only one of these methods.

In an ecological protocol, we asked native-German speakers to listen to Hindi stimuli (it was their first exposure to that language) and imitate/repeat aloud what they have just listened. They had only one opportunity to repeat aloud the sentences or word they listened, without rehearsal, which assured that the task was measuring pure foreign-language imitation and repetition. We then carried out a correlation between the performance scores obtained in the Hindi-imitation task and the fractional anisotropy and volumetric values extracted after the dissection of the arcuate fasciculus.

This is the first time to our knowledge in which foreign-language imitation is studied in such an ecological way and correlated with white-matter microstructure. Based on previous reports, we expected that the microstructural organization of the left arcuate fasciculus would predict the performance in foreign-language imitation, although we did not discard a possible involvement of the right arcuate fasciculus (due to imitation-strategies based on prosodic cues).

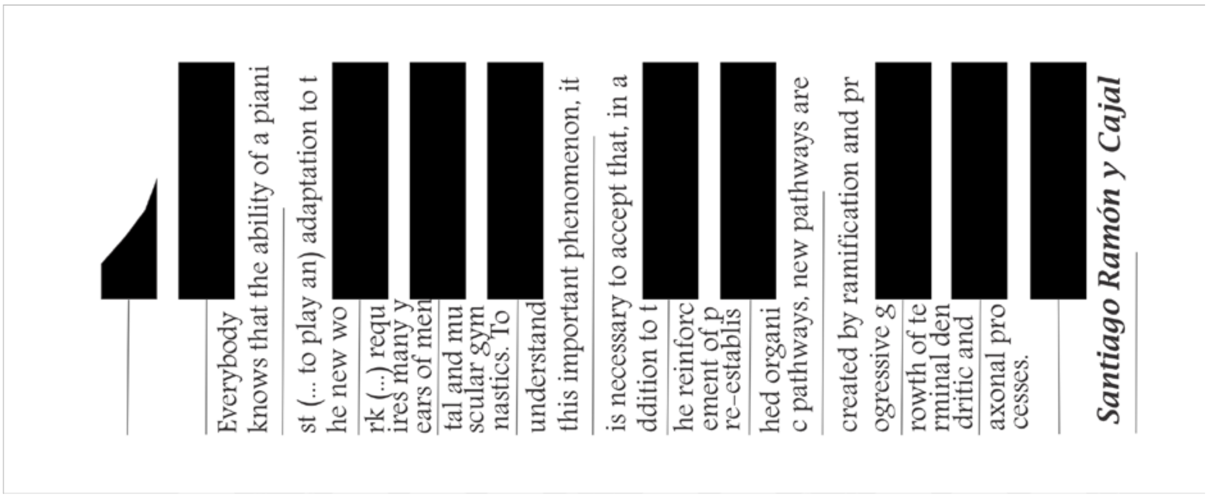
2.3 Study III: White-matter connectivity predicts music skills in non-musicians

The third experiment aimed to study the white-matter microstructural substrates related to music learning in non-musicians. Specifically, we were interested in investigating whether the microstructural organization of some auditory-motor- and sensorimotor-related white-matter tracts, previously described as crucial for music practice and showing neuroplastic effects in musicians (i.e., the corticospinal tract and the arcuate fasciculus), would be able to predict individual differences in music abilities.

We recruited a cohort of healthy native Spanish-Catalan participants without musical experience who completed both (i) a structural scan and, in a different day always after the MRI scan, (ii) a Fast Music Learning protocol, consisting on a Melody-learning task (Chen et al., 2012) and a Rhythm synchronization task (Bailey & Penhune, 2010; Padrão et al., 2014) that they have to master to their maximum capabilities in that single session. We used manual-deterministic tractography to dissect the arcuate fasciculus and the corticospinal tract, extracting the values of volume and fractional anisotropy and (Pearson) correlating them with learning and performance measurements from the musical tasks.

We expected to find markers of better white-matter microstructural organization in both tracts in relation to more accurate performance in the musical tasks. To our understanding, this is the first time that white-matter microstructural connectivity is measured via deterministic tractography and explored for its predictive value in regard to music learning and abilities in non-musicians.

Chapter 3 - Study I: Long-term neuroplastic effects in professional pianists[1]



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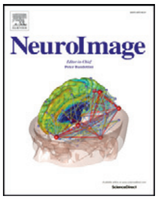

Structural neuroplasticity in expert pianists depends on the age of musical training onset

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ABSTRACT

In the last decade, several studies have investigated the neuroplastic changes induced by long-term musical training. Here we investigated structural brain differences in expert pianists compared to non-musician controls, as well as the effect of the age of onset (AoO) of piano playing. Differences with non-musicians and the effect of sensitive periods in musicians have been studied previously, but importantly, this is the first time in which the age of onset of music-training was assessed in a group of musicians playing the same instrument, while controlling for the amount of practice. We recruited a homogeneous group of expert pianists who differed in their AoO but not in their lifetime or present amount of training, and compared them to an age-matched group of non-musicians. A subset of the pianists also completed a scale-playing task in order to control for performance skill level differences. Voxel-based morphometry analysis was used to examine gray-matter differences at the whole-brain level. Pianists showed greater gray matter (GM) volume in bilateral putamen (extending also to hippocampus and amygdala), right thalamus, bilateral lingual gyri and left superior temporal gyrus, but a GM volume shrinkage in the right supramarginal, right superior temporal and right postcentral gyri, when compared to non-musician controls. These results reveal a complex pattern of plastic effects due to sustained musical training: a network involved in reinforcement learning showed increased GM volume, while areas related to sensorimotor control, auditory processing and score-reading presented a reduction in the volume of GM. Behaviorally, early-onset pianists showed higher temporal precision in their piano performance than late-onset pianists, especially in the left hand. Furthermore, early onset of piano playing was associated with smaller GM volume in the right putamen and better piano performance (mainly in the left hand). Our results, therefore, reveal for the first time in a single large dataset of healthy pianists the link between onset of musical practice, behavioral performance, and putaminal gray matter structure. In summary, skill-related plastic adaptations may include decreases and increases in GM volume, dependent on an optimization of the system caused by an early start of musical training. We believe our findings enrich the plasticity discourse and shed light on the neural basis of expert skill acquisition.

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Introduction

Professional musicians constitute an ideal group to study learning-related neuroplasticity (Schlaug et al., 1995; Münte et al., 2002; Gaser and Schlaug, 2003; Bengtsson et al., 2005; Bermudez et al., 2009; Imfeld et al., 2009) due to the intensity and scope of their training. Musical practice involves the development of fine motor skills, bimanual coordination, audio–motor integration, as well as cognitive processes, such as memory, attention and executive functions, all under the high motivational drive of the intrinsic emotional power of music (Schmithorst and Wilke, 2002; Zatorre et al., 2007; for a review see Jäncke, 2009 and Koelsch, 2010). Extensive musical practice during childhood and adolescence might have a strong effect on the development of brain structures. Importantly, this might be a bidirectional process: while music training promotes neuroplastic changes that enhance several underlying brain functions, this enhancement in brain structure and function might also improve music performance and learning (Pascual-Leone, 2001). Due to a high demand on bimanual dexterity, keyboard players have been a preferred group to study structural and functional brain changes (Amunts et al., 1997; Watson, 2006; Bangert et al., 2006). In a pioneering study, Schlaug et al. (1995) showed that professional musicians (pianists and string-players) had a larger middle section of the corpus callosum compared to a non-musician control group. Furthermore, those musicians who began their training before the age of 7 showed a larger anterior part of the corpus callosum compared to those with a late training onset. In a diffusion tensor imaging (DTI) study with pianists, Bengtsson et al. (2005) found that several white matter tracts correlated with the estimated amount of musical practice during childhood (e.g. posterior limb of internal capsule, the isthmus and the body of corpus callosum, and some fiber tracts in the frontal lobe), although the total number of practicing hours was lower in this period than the estimated hours in adolescence and adulthood. These results support the idea that the central nervous system exhibits greater plastic capacities during early stages of development and maturation periods, contrasting with its limited malleability during adulthood.

Previous studies have demonstrated the importance of the age of onset (AoO) of musical training in influencing brain plasticity. For instance, Amunts et al. (1997) affirmed that early musical training could lead to pronounced anatomical changes in the hand motor area. Similarly, a seminal magnetoencephalography (MEG) study (Pantev et al., 1998) showed that the dipole strength associated with piano tones was greater in the auditory network of those musicians who had begun practicing before the age of 9 years thus favoring the idea that the age of inception of musical training is important in determining the degree of cortical adaptation (Elbert et al., 1995; Amunts et al., 1997). The relevance of the AoO in relation to the performance level is generally confounded because early starters usually accumulate a larger amount of practice time. The relationship between sensitive periods and the level of expertise, and between these and the degree of anatomical predispositions or adaptations, is unclear at this point. Recent studies referring to one group of right handed early-onset and late-onset musicians show gray and white matter differences and enhanced timing skills in a finger tapping auditory–motor task in early-onset musicians. Via deformation-based morphometry, cortical gray matter differences in the right ventral premotor cortex were observed (Bailey et al., 2014), and using a novel multi-atlas automatic segmentation pipeline, smaller cerebellar gray matter volumes in the right lobule VI were shown (Baer et al., 2015). Using diffusion tensor imaging, Steele et al. (2013) found a higher fractional anisotropy in the isthmus of the corpus callosum. All of these morphological differences between the early- and late-onset groups correlated with their timing skills in an auditory–motor synchronization task using the right index finger: the earlier the start of music training, the better the performance in the synchronization task. In a recent study with selected highly trained pianists, Granert et al. (2011) measured the skill level of piano playing via the temporal accuracy during a scale-playing task. These authors found that the higher the skill level of piano playing, the smaller the volume of gray matter in the right middle putamen.

Broadening the concept of expertise, Gaser and Schlaug (2003) compared professional keyboard players, amateur keyboard players and non-musicians and reported increased GM volume in primary motor, somatosensory, and premotor areas, among other regions in the musician groups. James et al. (2014) applied a regression analysis over a three-group population modeling expertise in the same way as Gaser and Schlaug (2003), trying to find the areas in which professional musicians > amateur musicians > non-musicians (or vice versa) differed, while controlling for training intensity. They found an intricate pattern of increased/decreased GM. In particular, musicians showed GM density increases in areas related to higher-order cognitive processes (such as the fusiform gyrus or the inferior frontal gyrus), whereas GM decreases were found in sensorimotor regions (as perirolandic and striatal areas). These reductions in GM were interpreted as reflecting a higher degree of automaticity of motor skills in more expert musicians (James et al., 2014).

With the present investigation, we aimed to examine brain differences between a homogeneous group of selected musicians and a control group of non-musicians. In order to avoid any confounds, we restricted our analysis to extremely skilled and highly performing, award-winning concert pianists from the Hannover University for Music, Drama and Media. This is the first time that the effects of musical training depending on the AoO are addressed in such a homogeneous cohort of expert pianists, taking into account both AoO and amount of practice. Although previous literature seems to point to an improved neural system in musicians with a higher level of expertise (acquired after long periods of training), the results of studies either focusing on gray (Han et al., 2009) or white-matter differences (Oechslin et al., 2010) as a function of AoO of musical training are not clear cut. Thus, we divided the musician sample in pianists who began to play piano before age 7 (early) and after or at age 7 (late). This cutoff is widely accepted among plasticity researchers as a crucial age for starting musical training (Schlaug et al., 1995; Bengtsson et al., 2005; Steele et al., 2013; Penhune and de Villers-Sidani, 2014; Bailey et al., 2014; Baer et al., 2015; see reviews by Wan and Schlaug, 2010, and Penhune, 2011). Thus, the main goal of our study was to examine the effect of music training and age of onset in the GM structure of expert pianists. Voxel-based morphometry (Ashburner and Friston, 2000) was used and, based on previous literature, GM differences in areas related with motor, auditory and emotional processing were expected (see Table 1 for a summary of previous studies on neuroplasticity in musicians). Moreover, a scale-playing task was administered to the pianists in order to control for differences in performance skill between the early- and late-onset groups. Playing a scale on the piano is a demanding task, and the subtle timing differences detectable using this task have previously been shown to be a reliable and highly relevant indicator of pianistic expertise (Jabusch et al., 2009; van Vugt et al., 2014).

Materials & methods

Participants

Forty-one expert pianists and seventeen non-musicians participated in the study. All participants (both pianists and non-musicians) reported to be right-handed. Five participants from the pianists group were removed from the final analysis due to strong motion artifacts, thus leading to a final group of 36 musicians split into early (age of onset < 7 years; $n = 21$, 12 females; 15 caucasians, 6 asians) and late starters (age of onset ≥ 7 years; $n = 15$, 7 females; 12 caucasians, 3 asians). AoO of piano playing between early- and late-onset pianists was significantly different ($p < .001$). On the one hand, musicians were either advanced master-class piano students or professional pianists having graduated with piano as a major from the Hannover

University of Music, Drama and Media. A comparable high level of musical proficiency and expertise was assured by the fact that the entrance examination is extremely competitive, with an admission rate for the piano-master program of 1% to 5% depending on the year. Furthermore, all but two of our pianists had won national youth awards (such as the "Jugend Musiziert" or the "Steinway Young Artists Award"), and 14 had won prestigious international piano awards (in competitions such as the Van Cliburn–U.S.A., the Busoni–Italy, the Chopin–Warsaw, or the Leeds Piano–UK). To further ensure a similar level of musical proficiency and expertise, pianists had to fill a self-report that allowed us to calculate: the total hours of lifetime practice, the mean hours of practice during the previous week as well as the number of hours of practice per week during the last year. These three parameters of practice were compared between groups and no significant differences were found (significance for the difference between early-onset and late-onset pianists groups was superior to $p = .3$). On the other hand, non-musician controls were technical engineering and medicine students ($n = 17$, 7 females: all caucasians), and had no musical experience aside from the music lessons received in primary and secondary school. Further demographic and practice details are given in Table 2. The study was approved by the Ethics Committee of the MHH (Medical School of Hannover). All participants gave written informed consent, had no contraindications concerning an MRI scan (including seizure disorders, tinnitus, claustrophobia or hearing impairment) and reported no previous or current neurological or psychiatric disease.

Imaging data acquisition & preprocessing

Images were obtained with a 3-T magnetic resonance imaging (MRI) scanner (Siemens Allegra Magnetom Scanner, INI, Hannover, Germany). Conventional high resolution structural images [magnetization-prepared, rapid-acquired gradient echoes (MPRAGE) sequence, 192 slice sagittal, TR = 16 ms, TE = 4.9 ms, 1 mm thickness (isotropic voxels)].

Voxel-based morphometry

Voxel-based morphometry (VBM; Ashburner and Friston, 2000) was performed using MATLAB version 7.8.0 (The MathWorks Inc, Natick, Mass) and statistical parametric mapping software (SPM8; The Wellcome Department of Imaging Neuroscience, London). Specifically, the New Segment tool from SPM8 (an improved version of the 'unified segmentation' algorithm; Ashburner, 2012) was applied to the structural T1-weighted images to separate the different types of tissues. During this segmentation step, the ethnic differences of the participants were taken into account by specifying whether the affine regularization had to be done applying the values for the ICBM space template for East Asian brains or for European brains. After that, the resulting tissue probability maps (GM) were subjected to DARTEL (Ashburner, 2007) to achieve spatial normalization into MNI space. DARTEL normalization alternates between computing an average template of GM segmentation from all subjects and warping all the subjects' GM tissue maps into a better alignment with the template created (Ashburner, 2009). Normalized images were modulated by their Jacobian determinants in order to identify regional differences in the volume or amount of GM; "modulation" is used in order to try to compensate for the effect of spatial normalization, Mechelli et al., 2005. These normalized and modulated images were smoothed by using an isotropic spatial filter (FHWM = 8 mm) to accommodate for residual inter-individual variability.

The individual smoothed GM images were entered into a second-level analysis employing a random effects analysis within the general linear model. In order to compare musicians and non-musicians, a two sample t-test was calculated. Total volume of GM was included as a nuisance variable to correct for global differences in GM (Buckner et al., 2004). Moreover, an implicit absolute masking with a threshold of 0.2 (i.e. only those voxels having a 20% probability of being GM are included) was also used (Ashburner, 2010) in order to select only the most homogeneous voxels and to avoid potential problems around the boundaries between gray and white matter (James et al., 2014). Unless mentioned otherwise, contrasts are reported at whole-brain $p < .05$ FWE corrected threshold at the voxel level with a cluster extent of more than 50 contiguous voxels, thus effectively controlling for multiple comparisons.

All the results will be referred as differences in volume or amount of GM, which are terms consistent with previous VBM literature using similar analyses of T1 images (in which GM and white-matter normalized images were modulated by the Jacobian determinants derived from the spatial normalization step. Ashburner, 2010). However, it is important to note that the terms "amount of GM" or "GM volume" are not referring to the actual volume of tissue or amount of neurons. The maps created by SPM during the segmentation process represent the probability of GM found in each voxel, and therefore our analysis focused on the differences in signal intensity across voxels. The authors of the present study are aware of this constraint but decided to use the classic VBM terminology in order to make our results more easily accessible to the VBM community.

Correlation analysis

After exploring the results between pianists and non-musicians, we decided to investigate potential differences among the pianists group depending on the AoO of musical practice. We applied two different approaches: (i) On the one hand, we performed a between-group analysis comparing early-trained and late-trained pianists at whole-brain level in the same fashion as the one applied to compare musicians and non-musicians (two sample t-test, adding total volume of GM as a nuisance variable, and using an implicit absolute mask thresholded at 0.2). (ii) On the other hand, we saved each individual cluster obtained in the comparison between pianists and non-musicians as a mask. Then, we calculated the mean GM value for each subject in every cluster-mask in order just to check (in a descriptive way) the mean GM distribution among the three groups of subjects: early-onset pianists, late-onset pianists and non-musicians. Only for some particular areas of interest (putamen, see the explanation in the Results section) Pearson's correlations between mean GM volume within those particular structures and the AoO were computed. Unless mentioned otherwise, correlations are reported at an uncorrected $p < .05$ threshold.

Behavioral measurement of piano performance

In order to obtain an objective measurement of the level of piano performance in our pianists, we assessed temporal precision during a scale-playing task. However, due to practical restrictions, not all the pianists in the VBM sample completed this task: only the data from 15 early-onset and 13 late-onset pianists was acquired.

Participants played on a Kawaii MP9000 stage piano connected to a Pioneer A109 amplifier. The MIDI data was captured through an M-Audio MIDI-to-USB converter and fed in to a Linux-PC running a custom developed C program that captured the MIDI events. Before starting the task, the participants were invited to warm up and get used to the equipment by playing without guidance. After a few minutes, they began the scale exercises, which are explained in detail below. The exercises were presented visually as a musical score with indicated (standard) fingering. The pianists were asked to play as regularly as possible at a comfortable mezzo-forte loudness and in legato style. The entire procedure took about half an hour, and the pianists received a nominal financial compensation. Participants played two-octave piano scales accompanied by a metronome at 120 BPM. They played four notes within a metronome beat, i.e., eight keystrokes per second. They played blocks of approximately 30 alternating ascending and descending scales with a 9-note rest in between (to ensure alignment of the beginning of the scale with the metronome). The scales were played in the following blocks, separated by small breaks: (i) C-major scale with the right hand only, (ii) C-major with the left-hand, (iii) A-minor with the right hand, (iv) F#-major with the right hand, (v) C-major with both

Table 1
Summary of previous neuroplasticity studies with musicians. Techniques, participants and results are detailed.

Reference	Type of study	Subjects	More salient results
Schlaug et al. (1995)	MRI: morphometric analysis	Musicians ($n = 30$) vs. non-musicians ($n = 30$), & musicians between them	- Larger anterior CC in musicians compared to non-musicians, especially those who began musical training before age 7.
Amunts et al. (1997)	MRI: morphometric analysis (study of the depth and length of the central sulcus)	Musicians (keyboard students, $n = 21$) & non-musicians ($n = 30$)	- Greater symmetry of ILPG in musicians, due to greater ILPG in the right hemisphere. - Strong negative correlation between the time at which musical training started and the right and left ILPG. - More symmetrical and superior distal finger performance (tapping) in musicians compared with controls.
Pantev et al. (1998)	MEG	Musicians with AP ($n = 9$), musicians with RP ($n = 11$) & non-musicians-controls ($n = 13$)	Strength of cortical activation higher in response to piano tones and in musicians who began practicing before the age of 9.
Pascual-Leone (2001)	TMS	Non-musicians	Cortical output maps showed an increased expansion during the beginning of a practice period in the contralateral M1 area (*after musical training*).
Schmithorst and Wilke (2002)	MRI–DTI	Musicians ($n = 5$) vs. non-musicians ($n = 6$)	In musicians: Among several areas found, the FA values within the internal capsule were significantly smaller, while the FA values in the genu of the CC were significantly greater.
Schneider et al. (2002)			Greater GMV in the anterior-medial portion of Heschl's gyrus in musicians compared to non-musicians.
	MEG & MRI	Non-musicians ($n = 12$), professional ($n = 12$) & amateur musicians ($n = 13$)	GMV and signal amplitude in HG correlated positively with musical aptitude, and were higher in musicians.
Gaser and Schlaug (2003)	MRI–VBM (GM volume)	Professional ($n = 20$) & amateur musicians ($n = 20$) & non-musicians ($n = 40$)	GM highest in professional musicians, intermediate in amateurs musicians and lowest in controls. Areas related to musician status (professional musicians > amateurs > non-musicians): primary motor, premotor and somatosentory areas, ant. sup. parietal, inf. temporal gyrus, left cerebellum, left HG, and left inf. and right medial frontal gyrus.
Hutchinson et al. (2003)	MRI–VBM	Musicians, keyboard players ($n = 60$) vs. non-musicians ($n = 60$)	Male musicians ($n = 30$): Higher absolute and relative cerebellar volume; relative cerebellar volume correlated with intensity of practice. More GM in the right hemisphere in: frontal & prefrontal lobe, sup. temporal lobe, inf. & medial temporal gyrus, temporal pole, sup. pre- and postcentral gyrus, sup. & inf. parietal lobe, cuneus, cingulate and lingual gyrus.
Luders et al. (2004)	MRI–VBM	Musicians: non-AP ($n = 40$) & with AP ($n = 20$)	More GM in the left hemisphere: sup. Temporal gyrus (HG), PT, inf. pre- & postcentral gyrus, mesial frontal lobe, thalamus, caudate and occipital pole. - *Childhood practicing* correlates positively with FA in: bilateral PLIC, CC, fiber tracts in sup. & inf. frontal lobe.
Bengtsson et al. (2005)	MRI–DTI	Musicians, pianists ($n = 8$) vs. non-musicians ($n = 8$)	- *Adolescence practicing* corr. positively with FA in: the splenium and the body of CC. - *Adult practicing* corr. positively with FA in: left ant. limb of the internal capsule, fiber bundle in right temporoparietal junction (arcuate fasciculus).
Schneider et al. (2005b)	MEG–MRI	Musicians (professionals: $n = 51$, amateur: $n = 16$) & non-musicians ($n = 20$)	Enhanced functional response and enlarged GM in the HG in professional musicians compared to non-musicians (corr. with musical aptitude). Structural and functional leftward lateralization for fundamental pitch listeners (as pianists or percussionists), rightward lateralization for spectral pitch listeners (as string players or singers).

(continued on next page)

Table 1 (*continued*)

Reference	Type of study	Subjects	More salient results
Bangert et al. (2006)	fMRI (task: listening/pressing piano keys)	Musicians, pianists ($n = 7$) vs. non-musicians ($n = 7$)	- *Acoustic task*—higher activity in:right SMA, left precentral, bilat. middle temporal gyrus, left STG, left Broca's area & left inf. parietal lobule. - *Motion-related task*: bilateral prefrontal & precentral gyrus, right SMA, right middle temporal, right HPC & left PHPC, right supramarginal, right cingulate, left STG & Broca's area. - *Conjunction*: Left-hemisphere network in musicians (involving frontal, temporal, parietal areas, & language regions of the cerebral cortex).
Bermudez et al. (2009)	MRI–VBM & cortical thickness	Musicians ($n = 71$, 27 of them with AP) vs. non-musicians ($n = 64$)	- *Musicians vs. controls* (areas of convergence among methods: VBM & Cortical thickness): greater GM and thickness in superior temporal (more on the right); greater cortical thickness in BA 44/45 and 47; greater GM and thickness in sup. central sulcus.
Han et al. (2009)	MRI–VBM (GM Density) & DTI	Musicians-pianists ($n = 18$) vs. non-musicians ($n = 21$)	Musicians > non-musicians: *GM density*: higher in left sensorimotor cortex and right cerebellum; lower in right OFG and left ant. cingulate cortex. *FA*: higher in the right PLIC and midbrain, & left inf. frontal gyrus.
Imfeld et al. (2009)	MRI–DTI (study of CST)	Musicians ($n = 26$, 13 of them with AP & 13 without AP) vs. non-musician controls ($n = 13$)	- Lower mean FA values in left and right CST for musicians. - Mean diffusivity values correlated with onset of musical training in the CST, and other fiber structures (higher diffusivity for earlier onset).
Oechslin et al. (2010)	MRI–DTI (study of SLF)	Professional musicians with AP ($n = 13$), professional musicians without AP ($n = 13$) & non-musician controls ($n = 13$)	- Left-greater-than-right lateralization in FA values in AP-musicians. - High performance in the AP-test correlates with low mean FA values. - But no significant lateralization effect as a function of musical expertise.
Steele et al. (2013)	MRI–DTI + TMST	Early-trained musicians ($n = 18$, AoO: before age 7), late-trained musicians ($n = 18$, AoO: after age 7), & non-musicians ($n = 17$)	- Synchronization and performance of TMST was better in ET, intermediate in LT and lower in NM. Synchronization of the TSMT was correlated with FA in the left temporal lobe, extending to posterior limb of internal and external capsules. - ET showed greater FA than LT in posterior midbody / isthmus of CC. - AoO significantly correlated positively with FA (in the CC and temporal regions) and negatively with RD (in temporal regions).
Bailey et al. (2014)	MRI: morphometrical analyses (VBM, DBM & cortical thickness) + rhythm synchronization task (RST)	Early-trained ($n = 15$, AoO: before age 7), late-trained musicians ($n = 15$, AoO: after age 7) & non-musicians ($n = 20$)	- *RST*: ET outperformed NM, but not LT in performance measures. In ITI deviation, ET outperformed LT, and both groups outperformed the NM. - *VBM & DBM overlapping results*: ET showed more GM and more deformation in right vPMC, compared to LT. - Deformation values from right vPMC *correlated with AoO* and performance in RST.
James et al. (2014)	MRI: morphometrical analysis (VBM: relation with expertise)	Professional ($n = 20$) & amateur pianists ($n = 20$), & non-musicians ($n = 19$)	- *GMD increases with expertise in*: right fusiform gyrus, right mid orbital gyrus, left inf. frontal gyrus, left intraparietal sulcus, bilateral cerebellar Crus II & left HG. - *GMD decreases with expertise in*: bilateral perirolandic and striatal areas. - GMD in the righ mid orbital area and the IFG predicted accuracy in detecting fine-grained incongruities in tonal music.
Baer et al. (2015)	MRI (multi-atlas segmentation pipeline)	Musicians ($n = 38$) & non-musicians ($n = 20$)	- ET showed reduced WM volume bilaterally compared to LT. - ET showed reduced WM volume in lobules IV, V and VI compared to LT. - Better timing performance, greater musical experience and earlier age of start were associated with smaller cerebellar volumes. - Better timing performance was associated with smaller WM volumes of the right lobule VI.

Summary of some previous findings in musicians. Abbreviations: *Techniques and parameters*: MRI: magnetic resonance imaging, MEG: magnetoencephalography, DTI: diffusion tensor imaging, fMRI: functional MRI, FA: fractional anisotropy, VBM: voxel-based morphometry, GM: gray matter, GMD: gray matter density, GMV: gray matter volume, WM: white matter, RST: rhythm synchronization task, ITI: inter-tap interval, TMST: temporal motor sequencing task, corr.: statistically correlated/correlating. *Musicians' traits*: AP: absolute pitch, RP: relative pitch or non-AP, ET: early-trained musicians, LT: late-trained musicians, NM: non-musicians. *Areas*: CC: corpus callosum, ILPG: intrasulcal length of the precentral gyrus, HG: Heschl's gyrus, PLIC: posterior limb of internal capsule, SMA: supplementary motor area, BA: Brodman's area, PT: planum temporale, OFG: orbitofrontal gyrus, CST: corticospinal tract, SLF: superior longitudinal fasciculus, vPMC: ventral premotor cortex, HPC: hippocampus, PHPC: parahippocampus, sup.: superior, inf.: inferior, mid.: middle, ant.: anterior, post.: posterior.

Table 2
Main characteristics of the sample (musicians and non-musicians). Mean and s.d. (standard deviation) are shown.

Characteristics	Early-onset pianists	Late-onset pianists	Control subjects
N	21	15	17
Mean age	24.90 (s.d. 4.89)	23.60 (s.d. 3.62)	24.06 (s.d. 4.39)
Ethnics	15 caucasians, 6 asians	12 caucasians, 3 asians	17 caucasians
Gender	12 females, 9 males	7 females, 8 males	7 females, 10 males
Mean age of musical exposure	5.19 (s.d. 0.69)	8.33 (s.d. 1.98)	---
Total hours of practice	14853.48 (s.d. 9294.13)	12366.67 (s.d. 7668.25)	---
Mean hours of practice last week	14.26 (s.d. 9.31)	15.49 (s.d. 11.18)	---
Hours of practice last year	19.92 (s.d. 12.27)	19.13 (s.d. 14.91)	---

Summary of the demographical traits of the sample. There was no significant difference in age between the three groups (significance for the difference between the three groups regarding age was superior to $p = .3$). Age of onset between early- and late-onset pianists were significantly different ($p < .001$). However, there were no significant differences in the amount of practice between both groups of pianists: Total hours of practice: $p = .387$; Mean hours of practice per week: $p = .720$; Hours of practice last year: $p = .864$.

hands. In the current study, we only analyzed the C-major scales for left and right hand (condition i and ii). The collected dataset was also included in a previously published study (van Vugt et al, 2012).

We then proceeded to calculate the temporal unevenness of the keystrokes by taking the SD of the inter-keystroke-intervals (medianSD-IOI in milliseconds) in each scale run and then averaged for all runs in each playing direction (ascending, descending). The higher this value, the more irregular the timing of the keystrokes, indicating poorer timing control. The medianSD-IOI has been employed previously (Wagner, 1971; MacKenzie and van Eerd, 1990; van Vugt et al, 2012).

After obtaining timing unevenness measures for each hand, 4 different analyses were performed: (i) a between-group comparison in order to check for potential differences in timing unevenness between the early-onset and the late-onset groups of pianists; (ii) Pearson's correlations between timing unevenness in each hand and the AoO (2 correlations); (iii) using the same masks applied for the correlation between GM volume and AoO, Pearson's correlations between the GM values inside these masks (i.e., bilateral putamen) and the timing unevenness for each hand (4 correlations); (iv) we repeated the correlation between the GM volume inside each VBM mask (right and left putamen) and the AoO, but this time controlling for the timing unevenness in each hand (4 partial correlations). Unless mentioned otherwise, correlations are reported at an uncorrected $p < .05$ threshold.

Results

Between-group comparison: pianists vs. non-musicians

The between-group analysis showed that musicians presented greater GM volume than non-musicians in the basal ganglia, specifically in the putamen bilaterally, extending to part of the anterior hippocampus, the pallidum and the amygdala—specifically the superficial and medial nuclei, the central nuclei and the laterobasal amygdala (identification based on descriptions by Snell, 2001; and Koelsch, 2014; and using the WFU-Pickatlas software, ANSIR—Advanced NeuroScience Imaging Research Laboratory, Department of Radiology of Wake Forest University School of Medicine, Winstom, Salem, NC; Maldjian et al., 2003, 2004; Lancaster et al., 1997, 2000; Tzourio-Mazoyer et al., 2002) and in the right thalamus (particularly, in the ventral posterolateral and lateral posterior nuclei, as well as in parts of the dorsomedial and the pulvinar regions; based on Behrens et al. (2003)and Johansen-Berg et al. (2005)), as well as in the bilateral lingual gyri and the left superior temporal gyrus. In addition, pianists showed a reduction in GM volume in the right supramarginal, right postcentral and right superior temporal gyri as compared to non-musicians (see Table 3 and Fig. 1A and C).

Table 3
Areas showing differences in the VBM analysis (gray matter volume) between the whole group of musicians and the non-musician control group.

Area	Hemisphere	Cluster size (mm3)	*T* value	Peak coordinates *x*	*y*	*z*
Pianists > non-musicians						
HPC–Putamen	L	849	8.25	−29	−10	−12
Amygdala	L			−18	−3	−14
Calcarine sulcus	R	1716	7.79	6	−88	−0
Lingual gyrus	R			6	−78	−11
Putamen	R	815	6.78	29	2	−3
Thalamus	R	341	6.48	14	−25	−3
STG	L	60	5.86	−47	−1	−11
Pianists < non-musicians						
Supramarginal	R	1813	7.67	66	−21	19
STG	R			63	−24	3
PCG	R			69	−13	39

Results of the VBM analyses of T1 images (gray matter volume). Table shows the areas that show differences in both directions, pianists > non-musicians and pianists < non-musicians, at a whole-brain FWE corrected $p < 0.05$ with 50 clusters of spatial extent. Peaks coordinates are given following the MNI system. Abbreviations: HPC, hippocampus; STG, superior temporal gyrus; PCG, postcentral gyrus; L, left hemisphere; R, right hemisphere.

Exploring differences depending on the age of onset of piano playing

Between-group comparison: early-onset vs. late-onset pianists

A between-group analysis comparing early-trained and late-trained pianists at whole-brain level was performed in the same fashion as the one carried out to compare musicians and non-musicians. However, no significant differences were found between the two groups of pianists at a whole-brain level, with a *p*-value < .05 FWE corrected threshold at the voxel level, with a cluster extent of more than 50 contiguous voxels.

Correlation analysis

In order to investigate potential individual differences among the pianist groups using another analysis, we obtained a mask for every significant cluster of the between-group comparison between pianists and non-musicians. We then calculated the mean GM value for each subject in every cluster-mask to check the distribution among the three groups of subjects: early-onset pianists, late-onset pianists and non-musician. As a merely descriptive measure and only for visualization purposes, the distribution by group for each significant cluster is depicted in Fig. 2 and the mean GM volume values for every cluster are detailed in Table 4. The mean GM values in the two clusters in the putamen (from the contrast pianists > non-musicians) showed the largest difference in plain sight between the two groups of pianists (*mean GMV in the left putamen*: early-onset pianists = 0.454, late-onset pianists = 0.473, and non-musicians = 0.425; *mean GMV in the right putamen*: early-onset pianists = 0.515, late-onset pianists = 0.539, and non-musicians = 0.478). These clusters were qualitatively selected: no between-group comparison or statistical analysis was performed. Thus, a Pearson's correlation analysis was calculated between the AoO of piano playing and the mean GM value for each musician solely inside right and left putamen cluster-masks. Only the mean GM volume in the right putamen showed a significant positive correlation with the AoO of piano playing ($r = 0.36$, $p = 0.03$). Meaning that the later the age of

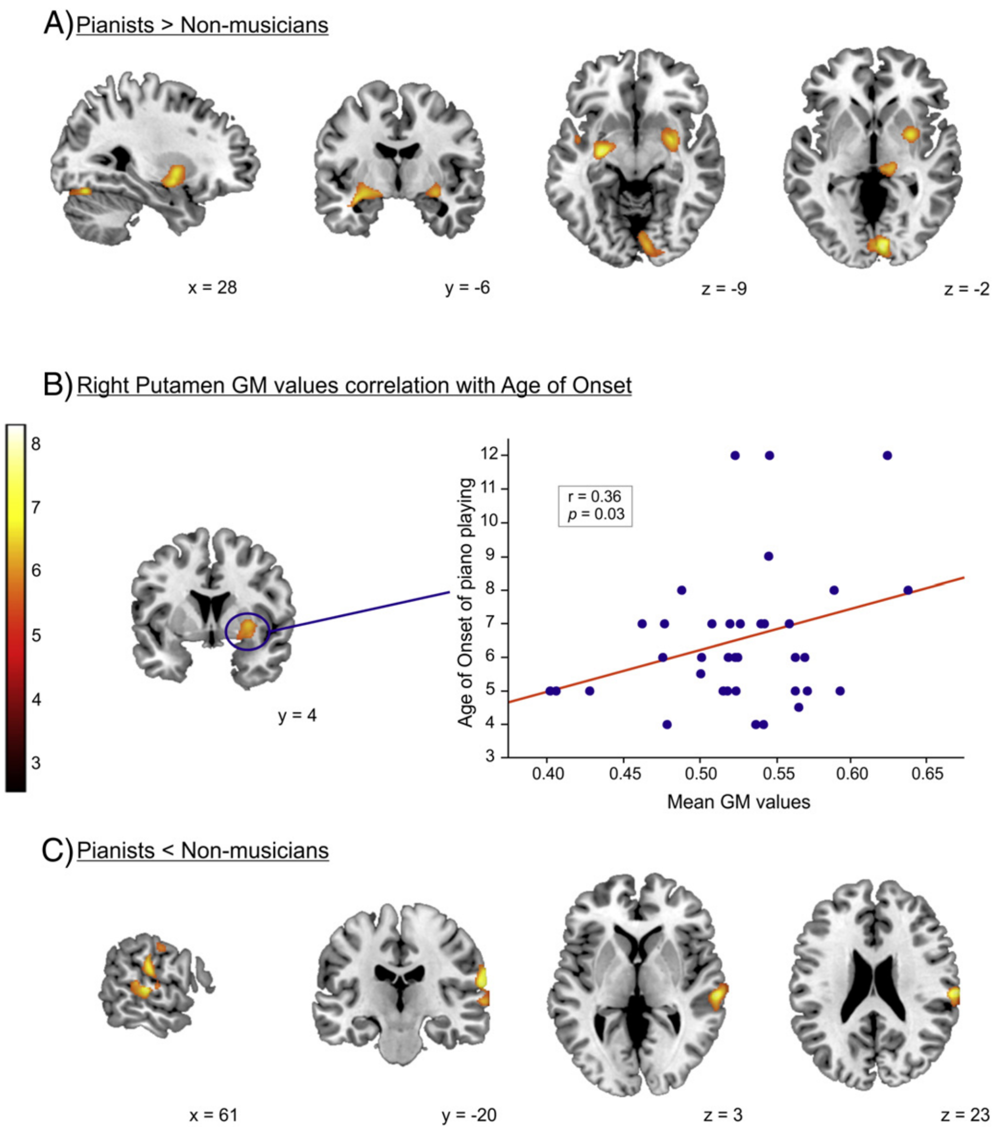

Fig. 1. VBM results: Between-group comparison and correlation with age of onset. A. Pianists > non-musicians: compared to non-musicians, musicians presented greater GM volume in basal ganglia, specifically in the putamen bilaterally (extending also into hippocampus, pallidum and amygdala, among other near-by structures) and in the right thalamus, as well as in the bilateral lingual gyri and the left superior temporal gyrus. B. Right putamen GM values correlation with age of onset: the right putamen was the only area that correlated significantly with the AoO of piano playing. This positive correlation means that the later the age of start of piano playing, the greater the GM volume in the right putamen. C. Pianists < non-musicians: pianists showed less GM volume in the right supramarginal, postcentral and superior temporal gyri as compared to non-musicians. Abbreviations: VBM: voxel-based morphometry; AoO: age of onset of piano playing; GM: gray matter.

start of piano playing, the greater the GM volume in the right putamen (see Fig. 1B).

Piano playing performance

From the scale playing recordings, we discarded scales that were played incorrectly (2.44% of the recorded material) and analyzed the remaining 31.0 (SD = 1.9) scale runs.

Between-group comparison: early-onset vs. late-onset pianists

A between-group comparison for the scale-playing timing unevenness (medianSD-IOI) in each hand was carried out in order to check for behavioral differences in piano playing between early-onset and late-onset pianists. We performed an ANOVA with timing unevenness (medianSD-IOI) as dependent variable and within-subjects factor hand (left/right) and between-subjects factor age of onset (early/late). We found a main effect of hand (F(1,31) = 20.83, $p < .0001$) indicating that right hand scales were played more evenly. The main effect of AoO was significant (F(1,31) = 7.11, $p = .01$) indicating that early onset pianists played more evenly (mean = 10.35, SD = 2.19 ms) than late onset pianists (mean = 12.69, SD = 3.60 ms) (see Table 5).

Correlation analyses

Correlation between performance and age of onset. A positive significant (Pearson's) correlation was found between the timing unevenness of the left hand performance values and the AoO (r = 0.40, p = 0.03; see Table 5). This means that the later the onset of piano playing, the greater the temporal variability in scale-playing in the left hand.

Correlation with the GM volume in the putamen. We performed Pearson's correlations between the GM volume inside the putamen masks (left and right) obtained from the musicians vs. non-musicians VBM comparison (the same ones applied for the correlation between GM volume and AoO), and the measurements of performance for each hand. No significant results were found for the left- or the right-hand temporal variability measurements.

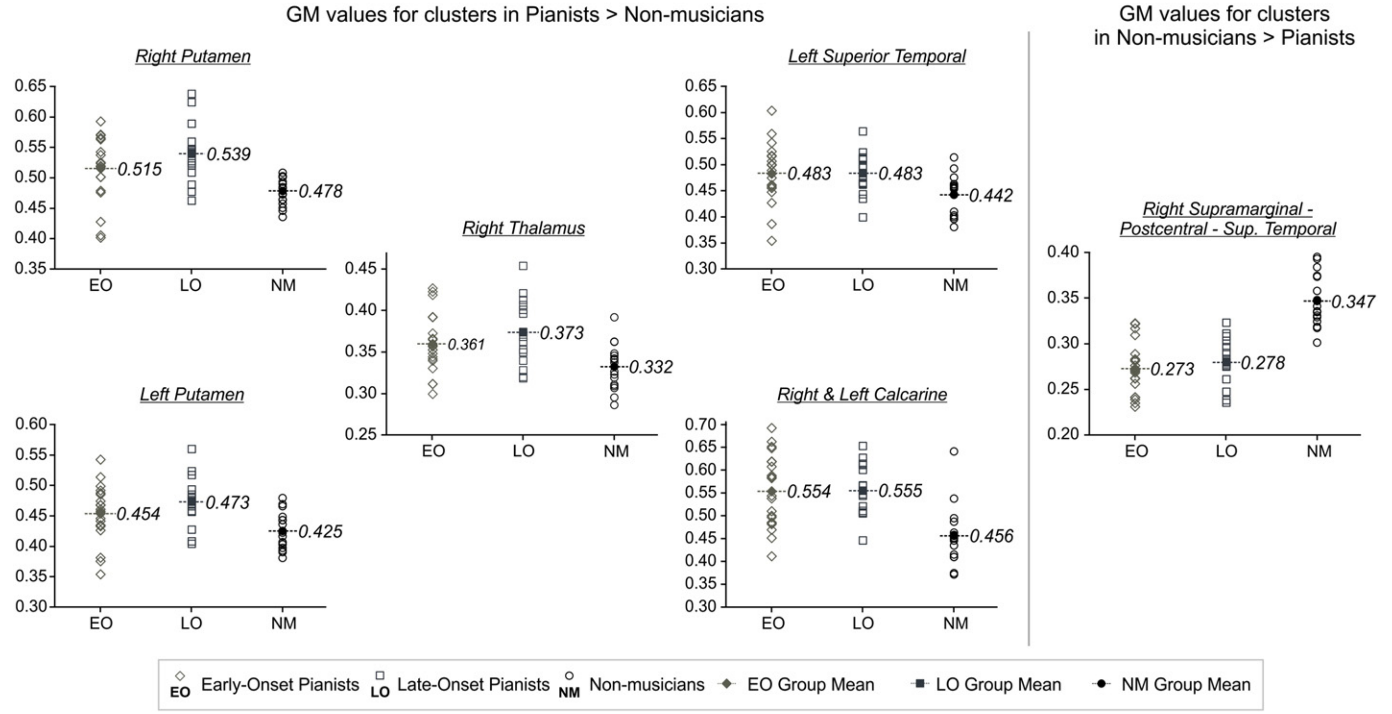

Fig. 2. Distribution of GM values by group and cluster. Distribution of GM values for each group (early-onset pianists, late-onset pianists and non-musicians) in each significant cluster obtained in the VBM analysis for the between-group comparison. Abbreviations: VBM: voxel-based morphometry; GM: gray matter.

Partial correlation between GM volume in the putamen and AoO, controlling for performance. In order to ensure that the positive correlation found between GM volume in the right putamen and the AoO could not be explained by the differences in performance found between early-onset and late-onset pianists, partial correlations between the GM volume inside each VBM mask (right and left putamen) and the AoO, controlling separately for left-hand and right-hand timing variability values, was carried out. We found that the significant positive correlation between AoO and the GM volume in the right putamen was still significant only when controlling for the timing variability in the left hand ($r = 0.39$, $p = 0.04$).

Discussion

The present study addressed brain structural effects of musicianship by comparing a highly select group of expert pianists with a non-musician control group. Taking into account that each instrument involves different muscles and techniques (eliciting plastic effects in different brain areas) and that previous studies have shown an influence of the type of instrument played on neuropsychological (Tervaniemi, 2009) and neurophysiological measures (Margulis et al., 2009; Gebel et al., 2013), we decided to include only expert pianists. To the best of our knowledge, this is the first time that the differences between musicians and non-musicians were studied in such a homogeneous sample (only expert pianists), taking into account both age of onset (AoO) and amount of practice, and also including a very precise and musically relevant behavioral test (i.e., scale-playing task) to assess performance level directly at their chosen instrument. The cutoff for the AoO was 7 years old (early-onset < 7 years, late onset ≥ 7 years) and there were no significant differences in the amount of hours of practice between early- and late-onset pianists. Our results will be discussed within the framework of plasticity effects induced by sustained and repetitive practice, considering also how neural efficiency due to intensive and long-term skill training could take place in the brain at different age periods.

Table 4
Mean GM values for the significant clusters obtained in the VBM comparison between pianists and non-musician controls.

	Early-onset pianists	Late-onset pianists	Control subjects
Contrast pianists > non-musicians			
Right putamen	0.515	0.539	0.478
Left putamen	0.454	0.473	0.425
Right thalamus	0.359	0.374	0.332
Left STG	0.483	0.483	0.442
Bilateral lingual gyrus–Calcarine	0.554	0.555	0.456
Contrast pianists < non-musicians			
Right Supramarginal–Postcentral - STG	0.273	0.278	0.347

Abbreviations: GM: gray matter; VBM: voxel-based morphometry; STG: superior temporal gyrus.

Structural effects of musicianship: Enlargements in GM volume

Current understanding of brain plasticity effects elicited by early training or early and intense lifetime experiences (either in form of enlargements or reductions of GM), as well as "normal" neural maturation, is still provisional and incomplete (Tau and Peterson, 2010; Zatorre, 2013). In the present study, highly skilled pianists showed greater GM volume in bilateral putamen compared to non-musicians, a part of the striatum that has been classically related to motor control and more recently to implicit sequence learning, reinforcement learning and memory-related processes (Packard and Knowlton, 2002; Graybiel, 2005; Carlson, 2012; Wilkinson and Jahanshahi, 2007). Basal ganglia is a region in which GM and white matter structural experience-related effects have been previously described in studies with other kind of experts (i.e., chess players: Hänggi et al., 2014; golfers: Jäncke et al., 2009). The effects observed in the basal ganglia in the present investigation might be surprising in comparison with those found in Granert et al. (2011) and James et al.'s (2014) studies, in which reductions of GM were found as a function of accurate performance and expertise. In the present study, however, we found an increase in GM volume in this structure in pianists compared to non-musicians. This effect could be explained by the fewer amount of hours practiced by our pianists

Table 5
Values of the measurements of scale-playing timing unevenness (medianSD-IOI in ms) by hand. Between-group comparison and correlation of the complete pianists group with the AoO.

Between-group comparison of timing unevenness					
	Early-onset pianists ($n = 15$)	Late-onset pianists ($n = 13$)	T-value	Degrees of freedom	Significance (p-value)
Left hand unevenness	10.82 ± 2.17	13.82 ± 3.85	2.59	26.00	0.016*
Right hand unevenness	9.47 ± 1.36	11.85 ± 3.05	2.60	16.07	0.019*

Correlation between timing unevenness and AoO		
	Mean (pianist whole group, $n = 28$)	Significance (p-value)
Left hand unevenness	12.21 ± 3.37	0.034*
Right hand unevenness	10.57 ± 2.56	0.115

Abbreviations: MedianSD-IOI: median standard deviation of the inter-onset interval; AoO: age of onset (of piano playing).
* Significant at an uncorrected p-value < .05.

compared to these previous investigations (present study's mean total life hours of practice: 13817.31 ± 8627.13, versus Granert et al.'s (2011) mean total life hours of practice: 36708 in dystonia patients/ 41684 in healthy pianists, although the pianists in the study were significantly older; the present study's mean hours per week in the last year: 19.59 ± 13.23, versus James et al. 's (2014) mean hours per week in the last age period measured for the expert musicians: 30.7 ± 8.5). As Poldrack et al. (2005) described, the basal ganglia (and the putamen in particular) is a structure related to motor skill automaticity, resulting from sequence motor training. Practice allows performance of well-known motor sequences as a single unit of activity, and this process causes a decrease (chunking) in activation in the areas related with sequence motor execution and knowledge. Previous studies (such as Granert et al., 2011, and James et al., 2014) showed a reduction of GM in striatal regions as a result of expertise, while here we found more GM in the putamen for the general comparison between musicians and non-musicians, but less GM as a result of an early onset of training among the pianists. It could be the case that the pianists in the present cohort presented a smaller degree of automaticity compared to pianists in previous studies, leading to this apparent discrepancy in the results. However, it is important to note that the present and previous research show a similar effect: the higher the motor efficiency in pianists (i.e., the smaller the temporal variability during playing), the smaller is the GM volume in the putamen, probably due to optimization processes such as pruning or more concise synapsing as a result of extensive practice during sensitive periods.

Significant differences were also found in other regions such as the hippocampus and amygdala, important structures relevant for emotional learning and memory consolidation (Blair et al., 2001; Maren, 1999; Amunts et al., 2005; Graybiel, 2000). More specifically, we found some significant voxels covering the anterior portion of the hippocampus. The anterior hippocampus has been related to novelty detection and associative learning (Mayes et al., 2007; Schinazi et al., 2013; Simó et al., 2015) and, interestingly, also to movement-related responses, reward or goal-directed functions and emotional memory (Strange et al., 2014). Important for the present results is also the involvement of the anterior hippocampus in the auditory domain, specifically in pitch processing and consonance/dissonance detection (Wieser and Mazzola, 1986; James et al., 2008). Finally, effects of musical expertise and auditory-specific training have been also found in the anterior hippocampus, both in musicians (James et al., 2008; Groussard et al., 2014) and in piano-tuners (Teki et al., 2012). In addition, we found differences in the superficial, medial, central and laterobasal nuclei of the amygdala. These nuclei are closely connected with the hippocampus, the dorsolateral thalamus and several cortical areas, such as the auditory cortices (Koelsch et al., 2008). The relationship between the amygdala and the auditory system has been highlighted in expert pianists performing a music expectation violation task (James et al., 2008), as well as in animal studies of fear conditioning and learning (Armony et al., 1998; Maren, 1999). Human studies suggest that the amygdala is not restricted to the processing of emotional or fear-related stimuli, but that it has a broader role in the detection of relevant stimuli (Sander et al., 2003), which might be important during the music-learning process. A circuit involving cortical structures, the amygdala, the hippocampus and the basal ganglia, has been associated with processing of emotional musical content (Koelsch, 2014). In addition, musical performance is associated with emotional and rewarding experiences (Zatorre et al., 2007) and it has been suggested that musicians construct particular memories relating to their musical experiences in a more detailed, emotional and vivid way than non-musicians (Groussard et al., 2014). Thus, based on previous studies, it is expected that other functions carried out by these regions, such as associative learning (Mayes et al., 2007; Schinazi et al., 2013; Simó et al., 2015), emotional memory (Strange et al., 2014) and pitch and auditory-expectancy discrimination (James et al., 2008; Teki et al., 2012; Groussard et al., 2014), might have been of great importance during the training of our expert pianists and, as a consequence, they could also explain the experience-dependent differences observed in musicians in comparison with non-musicians.

Enlargements in the volume of GM were also observed in the right thalamus, specifically in the ventral posterolateral and lateral posterior nuclei, and in parts of the dorsomedial and pulvinar regions. The thalamus acts as a crucial cortical-subcortical interconnectivity hub (Sherman, 2006); for example, the ventral posterolateral nucleus sends projections to primary somatosensory areas (Snell, 2001; see also Behrens et al., 2003; Johansen-Berg et al., 2005), relaying common sensations to consciousness. The dorsomedial nucleus has been associated with the integration of somatic information and subjective emotional states. Finally, the functional role of the lateral posterior and pulvinar nuclei is less clear, connecting with areas of the cerebral cortex such as premotor, primary and secondary somatosensory and temporal cortices.

Furthermore, greater GM volume was found in bilateral lingual gyri, a region linked to visual processing, dreaming (Bogousslavsky et al., 1987), visuo-spatial transformations of visual stimuli (Jackson et al., 2006) and word processing during reading (Price et al., 1997). Regarding the latter, the lingual gyrus is engaged in global shape processing and its activation is related to the length and visual complexity of the stimulus (not being specific to word processing; see Mechelli et al., 2000). Based on these evidences we suggest that this area might be involved in music-score reading and/or the visuo-spatial transformations needed to locate the read notes into the keyboard.

The last area found to be larger in pianists compared to non-musician controls was the left superior temporal gyrus, a cortical region containing the primary auditory area. Left auditory cortex has been discussed to have more precision than the right auditory area in processing rapid temporal changes (Zatorre, 2013; Schneider et al., 2005b). Although musical and fine grained pitch processing have been attributed to the right auditory cortex (Zatorre et al., 2002) and the only significant results we found in auditory regions were located at the left superior temporal gyrus, this left-hemispheric finding may be explained by the percussive character of piano sounds. Schneider et al. (2005a,b) found that fundamental pitch listeners – those who mainly decode the keynote or fundamental pitch of the stimuli (Schneider et al., 2005a) – present both greater GM volume and enhanced functional MEG activity in the left lateral Heschl's gyrus and showed a preference toward percussive or high-pitch instruments (such as piano, percussion instruments or guitar) compared to spectral pitch listeners. In addition, these authors also showed that 65% of the pianists in their sample were fundamental pitch listeners (Schneider et al., 2005b). Furthermore, effects of music practice were previously found in the left auditory cortex (Gaser and Schlaug, 2003; James et al., 2014).

Structural effects of musicianship: Reductions of GM volume

Pianists also presented some regions with a decreased GM volume compared to non-musician controls. Specifically, we found a reduced rightward cluster at the supramarginal gyrus, extending as well to the postcentral and superior temporal gyri. Several previous studies have shown that musical practice induces brain plasticity changes in the sensorimotor cortices (Elbert and Rockstroh, 2004; Jäncke, 2009). Hence, the postcentral gyrus, involved in the control of sensorimotor information (Kaas, 2004), is an area expected to show plastic effects due to the enormous tactile and motor stimulation that highly skilled pianists receive during their daily practice. This finding confirms a recent study (James et al., 2014), in which three groups of participants differing in their level of musical expertise showed reductions of GM density associated with greater expertise in the right postcentral gyrus. The right superior temporal gyrus, another area covered by this rightward cluster of reduced GM, contains the primary auditory cortex, but this hemisphere has been reported to be more sensitive to changes in fine grained pitch than its left homologue, causing an advantage for tonal functions (Zatorre et al., 2007). Consequently, it is generally assumed that the right auditory cortex is more involved in musical abilities and processing (Zatorre et al., 2002).

The supramarginal gyrus is part of the somatosensory associative cortex and has an important role in multisensory integration, body ownership and the location of the limbs in space (Carlson, 2012; Reed and Caselli, 1994; Berlucchi and Aglioti, 1997). Furthermore, this region has been related to language processing (Catani and Mesulam, 2008) and, interestingly for the present study, to music-score reading (Besson and Schön, 2001). In a PET study of sight-reading (reading and listening to a score simultaneously) Sergent et al. (1992) showed that the supramarginal gyrus, which was found active in both hemispheres, was involved in a visual-auditory mapping process. However, Stewart et al. (2003) and Stewart (2005) found activation in the left supramarginal gyrus after 3 months of musical training (score reading and piano playing) only when reading the scores, with no auditory stimuli. These authors attributed this activation to an automatic, learned association between the musical notation and the learned motor response (Stewart et al., 2003). In line with this interpretation, McDonald (2006) reported several problems in reading music scores and playing the piano after a stroke involving the right angular and supramarginal gyri. Some of the reported deficits were difficulties in reading the score when the notes were not assigned with their alphabetical name and incorrect placement of the notes on the keyboard. This evidence support the role of the supramarginal gyrus in music-score reading and, probably, in the motor preparation of the learned piano-playing response.

When one starts to play an instrument, visual, proprioceptive and auditory feedbacks are crucial; however, once the skill is acquired and one starts to master the instrument, neural systems may undergo a reorganization following the principles of economy (Krings et al., 2000; James et al., 2014), meaning that fewer neurons are recruited for the same processes. As Rypma and Prabhakaran (2009) proposed, when fewer nodes (individual neurons or functionally connected cell-assemblies) need to be crossed, the processing paths are more direct, the neural activity is reduced and the information processing is faster. As commented before, Poldrack et al. (2005) showed a reduction in activity associated with experience and training and proposed a chunking in the resources that leads to automaticity. These reductions in activity and tissue, such as the smaller volume found in our pianists, could be the result of an improved efficiency on the multi-sensory-motor pathways involved in long-term music training.

Behavioral relationship with scale-playing performance

We measured piano performance via a scale-playing task, calculating the timing unevenness (medianSD-IOI) for each hand during this task. We found a significant difference between early-onset and late-onset groups of musicians, evidencing that late-onset pianists present more timing variability during scale-playing. This is in line with previous reports, which have found better musical performance in early-trained musicians compared to late-trained musicians (Granert et al., 2011; Bailey and Penhune, 2012, 2013). In addition, and in line with this first result, we found a significant positive correlation between the performance of the left hand and the AoO of piano playing: the earlier the start of piano training, the better the performance of the left hand (the smaller the timing variability). We did not find any significant direct correlation between the GM volume in the putamen and the medianSD-IOI values, probably due to the small subsample of pianists that completed the scale-playing task. However, taking into account that both the GM in the right putamen and the performance of the left hand correlated positively with the AoO, our results might support previous findings (Granert et al., 2011). Granert et al. (2011) showed that early-onset pianists have both smaller volume of GM in the right putamen and higher skill-level of piano playing.

The link between our results regarding GM volume, the AoO and the performance values of the left hand, could suggest that the correlation found between AoO and GM volume in the right putamen might be explained by the differences in performance between early-onset and late-onset musicians. In order to rule out this option, we repeated the correlation between GM values in bilateral putamen and the AoO, but this time controlling for the performance in both hands (separately). We found that the correlation between GM volume in the right putamen and the AoO was still significant when controlling for the performance of the left hand, thus ensuring that the effects shown in the right putamen are due to the AoO of piano training and not to differences in skill level. We think that this correlation with GM in the right putamen only holds when controlling for the performance in the contralateral hand because this structure seems to be involved in motor control of the contralateral limbs, although there is still some debate regarding this laterality (Granert et al., 2011). Moreover, plastic effects in right motor-related structures as a consequence of improvement in left-hand motor performance have been previously reported after musical training (Hyde et al., 2009). These effects probably provide evidence that the left hand is the one which right-handed pianists have to practice more in order to control their performance, and the earlier they start to practice, the greater structural differences and the better overall control over their timing variability they accomplish.

Brain structural effects of age of onset of piano playing

All the pianists in our sample were highly skilled and currently practicing musicians, with a similar level of musical proficiency. However, as it has been discussed for language learning, similar proficiency levels do not directly inform about the implication of the same cognitive resources (Rodríguez-Fornells et al., 2009). Thus, we decided to investigate potential differences among the pianists group depending on the age of onset of musical practice, applying two different approaches. First, we performed a between-group analysis comparing early-trained and late-trained pianists at whole-brain level in the same fashion than the one applied to compare musicians and non-musicians. There were no significant differences between early- and late-onset pianists at a whole-brain p-value < .05 FWE corrected threshold at the voxel level, with a cluster extent of more than 50 contiguous voxels. The lack of significant results in this analysis could be explained by the small sample size of each group (early-onset pianists' $n = 21$, late-onset pianists' $n = 15$). Another possible explanation is that, since the two groups are highly skilled pianists, the differences could be too subtle to be detected at a whole-brain level.

Secondly, we carried out a Pearson's correlation between the AoO and the mean GM values of the right and the left putamen (those clusters from the comparison pianists > non-musicians which showed a qualitative higher difference between early- and late-onset pianists). A significant correlation was found at the right putamen: the later the onset of piano playing, the greater the volume of GM in this subcortical structure. Granert et al. (2011)recently reported that a low temporal precision (more temporal variability) in scale playing in professional piano players was associated with a larger volume of GM in the putamen. Previous reports show that early-onset musicians have better performance in musical-ability tasks (such as rhythm-learning tests: Bailey and Penhune, 2012, 2013) and motor-learning tasks (Watanabe et al., 2007) compared to late-onset musicians. This is also the case for the present study, at least for the subsample of pianists with measures of scale-playing performance.

The putamen has been reported to be crucial for the long-term storage of learned motor skills (Lehéricy et al., 2005), and it has been also related with temporal precision during piano playing and musical proficiency (Granert et al., 2011). Higher GM volume in the putamen of musicians could be interpreted as an index of better storage capacity for learned motor skills compared to non-musicians, although it should be kept in mind that music practice involves not only motor but an interaction of multi-sensorimotor and higher-cognitive functions (Jäncke, 2009; Herholz and Zatorre, 2012). Functions in the putamen could be refined when the training starts at an early age and would be demonstrated by a shrinkage in GM volume, which might explain the higher musical performance exhibited by early-onset musicians in previous reports (Granert et al., 2011; Bailey and Penhune, 2012, 2013) and in the present cohort. Moreover, less GM or white matter in the region of the basal ganglia in relation with greater experience, has been also described in other kind of experts after long-term training (chess players: Hänggi et al., 2014; golfers: Jäncke et al., 2009).

Late-onset pianists had to practice a large amount of hours in a reduced time window in order to obtain the same degree of proficiency as early-onset musicians; this intensive practice could have leaded to different patterns of brain reorganization as a function of the AoO. For instance, Sampaio-Baptista et al. (2014) observed that in a low-intensity group of juggling training, the performance was negatively associated with changes in GM volume in motor areas and the dorsolateral prefrontal cortex between a baseline MRI-scan and a second scan performed after 6 weeks of training. However, high-intensity jugglers showed a positive correlation between the pre- and post-training differences of GM volume in these areas and their juggling performance. This means that only high-practice elicited some plastic effects in direct positive relation with the achieved performance. Sampaio-Baptista et al. (2014) stated that, despite the fact that both groups presented the same level of performance, high- and low-intensity participants could be experiencing different stages of learning at the moment of the evaluation. Following this idea, the greater GM volume showed in the putamen by the late-onset pianist in our cohort could be interpreted as a consequence of an enormous practice in less time than the early-onset musicians. As mentioned above, our findings and previous reports together point out that early-onset pianists have both better motor skills and less volume in the putamen (Granert et al., 2011). Hence, the greater GM volume that the late-onset pianists present in this region may be taken as a 'predictor' for the lower skill-level of piano playing that they displayed behaviorally (see Results for the scale-playing test).

Plasticity and efficiency in music learning

Musicians have to practice accurate sequences of movements during a large period of time, in a training that implies integration of cognitive resources as well as a great amount of motivation. This daily routine might modify the synaptic efficacy and induce cortical and subcortical reorganization. In the present study we encountered greater GM volume in expert pianists in a network that might be involved in the learning and memorizing of auditory-motor material in presence of a high emotional content. On the other hand, we observed less GM volume in pianists in the right hemisphere in regions related to auditory-motor processing and practice, as well as with music-score reading. This decrease of GM could be interpreted as a sign of refined efficiency in a highly skilled and trained system. As it has been showed previously in animal studies (Kleim et al, 2004; Xu et al., 2009; Yang et al., 2009), dendritic spine refinement and circuit pruning are crucial processes in plastic phenomena. The present GM results could be puzzling and difficult to interpret, since all the areas found seem to be part of the same network or at least work together to accomplish functions that are involved in music training and piano practicing (Elbert and Rockstroh, 2004; Zatorre et al., 2007; Jäncke, 2009; Granert et al., 2011; James et al., 2014; Koelsch et al., 2008; Koelsch, 2014). However, we hypothesize that this pattern of increased GM volume in subcortical structures and decreased GM volume in cortical areas could be due to a balance-maintenance operation of the neural system: if some regions gain in volume or amount of GM, the same circuit should suffer a shrinkage in other regions to compensate and maintain the global volume of the network. Previous studies in literacy acquisition (Dehaene et al., 2015) have shown this kind of ‘recycling’ phenomena in some brain areas: after learning to read, the boundary between the left fusiform face area (FFA) and the visual word form area (VWFA) seems to shift, allowing more “space” for the VWFA (that is now needed for the new learnt skill); moreover, as literacy increases, the activity in the left FFA becomes smaller and seems to shift to the right hemisphere. Thus, in order to maintain the global balance of the visual system, the brain changes the structure and reorients some of its functions to preserve some of the old activities (i.e., face recognition) but allowing the new skill (reading) to take place and be stored in the brain. We suggest that a similar process could be taking place in this network involved in motor and emotional-reinforcement learning in our pianists. Moreover, we hypothesize that the AoO of piano playing could also influence how these plasticity effects get instantiated in the brain, leading to an even more efficient system in those pianists who started earlier in life.

The current most accepted hypotheses state that plasticity decreases with aging (Hallett, 1995), with several examples in the literature emphasizing the importance of plasticity during the first years of life (Schlaug et al., 1995; Amunts et al., 1997; Hyde et al., 2009; Imfeld et al., 2009). However, our knowledge regarding brain plasticity has been broadened in the last decades. Several examples in the literature showed reorganization of neural systems in different fields of expertise (i.e., musicians: Haslinger et al., 2004, athletes: Del Percio et al., 2009, chess-players: Hänggi et al., 2014, golfers: Jäncke et al., 2009), following a specific training (Maguire et al., 1997; Draganski et al., 2004; Poldrack et al., 2005), and also plastic adaptations as a consequence of a pathological state. For example, blind people (who are a good model of pathological reorganization due to the lack of sensory inputs in the visual modality) generally show shorter latencies of event-related potentials for auditory and somatosensory stimulations (Niemeyer and Starlinger, 1981; Röder et al., 2000). Furthermore, a recent fMRI investigation by Stevens and Weaver (2009) has highlighted the importance of critical periods in this population. In this experiment, Stevens and Weaver (2009) found that across all tonal stimuli (pure tones and frequency modulated ones) and comparing responses to silence, early-blind individuals showed substantially less signal in the auditory cortex, fewer active voxels, than late-blind and sight control participants. These authors argued that the decreased signal could be reflecting a greater processing efficiency. As they also remark, this hypothesis is supported by previous electrophysiological studies showing shorter latencies of early evoked potentials originated in the auditory cortex in early-blind individuals (Röder et al, 1996; Naveen et al., 1997, 1998; Manjunath et al., 1998), as well as the reduced metabolic responsiveness in a PET study of auditory localization with monkeys (Recanzone et al., 1993).

Functional neuroimaging studies have also revealed decreased cortical activation after long-term piano training, which has been taken as evidence for increased efficiency of the motor system and the need for a smaller number of active neurons to perform a determined set of movements (Krings et al., 2000; Jäncke et al., 2000; Haslinger et al., 2004). Ragert et al. (2003) conducted a tactile discrimination study in pianists in which they argued that metaplasticity processes (a higher-order form of plasticity related to the phenomenon of "learning to learn") are the substrate for the changes in neuronal efficacy induced by repetitive practice. Thus, it seems that sustained practice of a skill helps developing a state in which metaplasticity processes could enhance the learning induced plastic phenomena. Practicing routines in pianists could have helped developing this metaplastic state in neural networks, facilitating potential brain changes and promoting an altered efficiency of the sensorimotor, auditory and associative system. Furthermore, the existence of a sensitive period (Huttenlocher, 2003; Hensch, 2005) for music-skills acquisition has been proposed (Penhune et al., 2005; Bailey and Penhune, 2010) and has been supported by several morphometric studies (Steele et al., 2013; Bailey et al., 2014). Evidence for a critical period have been not only reported for the primary sensory systems (as the visual domain with experiments of monocular deprivation; Hubel et al., 1976; Shatz and Stryker, 1978), but also for language acquisition (Lenneberg, 1967). Although nowadays we probably describe this window of time, that extends from early infancy to puberty, as a sensitive period (Penhune, 2011), the concepts of neural plasticity, neurogenesis and brain repair have been redefined during the last years and the current picture of the adult learning brain is more dynamic (DeFelipe, 2006). All this information sheds some doubts on a rigid interpretation of the sensitive window hypothesis, even in language and music learning in adults (Rodríguez-Fornells et al., 2009; Penhune, 2011). However, starting to play an instrument early in life seems to have an advantage for auditory, motor, cognitive and associative systems. This advantage is probably due to the fact that training during sensitive periods (in which developmental plastic phenomena are taking place) may induce changes in the brain that might serve as a scaffold on which later training can build, enhancing the system (Steele et al., 2013).

Limitations

The present investigation may comprise some limitations, mainly associated with the structural neuroimaging analysis selected. VBM analysis presents several limitations that could affect the results and should be considered. First of all, during the segmentation process: on the one hand, because the model assumes that all voxels contains only one type of tissue, those voxels in the border and/or with a mixture of tissues may not be modeled correctly; on the other hand, tissue maps are created based on 'a priori' probability images, thus if a brain (due to its own special traits) cannot be adequately registered with the probability images, the segmentation will not be perfectly accurate (Ashburner and Friston, 2000). Secondly, in VBM various preprocessing steps (such as spatial normalization and smoothing of the images) are performed before any statistical comparison is carried out; the aim of these preprocessing steps is to make each brain more comparable to the rest of the group, but they should be done carefully in order to avoid losing the individual characteristics of each subject. Third, the threshold for the Gaussian kernel applied during the smoothing is inconsistent among different VBM studies, and it could affect the results (Ashburner and Friston, 2000). Fourth, as stated in the Materials and methods section, it is important to note as well that, although the terminology GM density and volume has been classically used to refer to VBM results, it should not be confused with actual measurements of cell packing density or volume of neurons that could be obtained via cellular or molecular techniques; one should keep in mind that VBM is only measuring voxel intensities (Ashburner and Friston, 2000), even though one uses the classic term 'GM volume' to explain the results, as in the present study. Fifth, great differences in the results could be obtained depending on the type of nuisance covariates used and the specifications applied to include them (Ashburner, 2010). Finally, Ashburner and Friston (Ashburner and Friston, 2000) stated that even with many hundreds of subjects in a database with controls, VBM may not be powerful enough to detect subtle differences among individuals. Furthermore, we think that depending on the amount and distribution of early- and late-onset participants in the sample of a study, different kind of findings could be obtained (for example, in the present study it would have been interesting to include more pianists in the range of age of onset between 9 and 12 years).

Conclusion

In the present investigation we found a complex pattern of increases and decreases in GM volume in several cortical and subcortical regions associated with musical practice (in line with previous findings: Stewart et al., 2003; Zatorre et al., 2007; Jäncke, 2009; Granert et al., 2011; James et al., 2014). Moreover, we found a significant positive correlation between the GM volume in the right putamen and the AoO of piano playing, even when controlling for the level of performance. We also found differences in the performance of piano practice between early-onset and late-onset pianists, and a significant correlation between performance of the left hand and the AoO. All these results indicate that the earlier the onset, the better the piano performance and the smaller the GM volume in the right putamen. The present results confirm some of the previous reports regarding plasticity effects induced by sustained and repetitive music practice (effects in somatosensory, motor, auditory, association and limbic regions). Moreover, we observed that neural efficiency due to intensive and long-term skill training seems to be determined by the age of commencement of musical practice.

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Conflict of interest

None declared.

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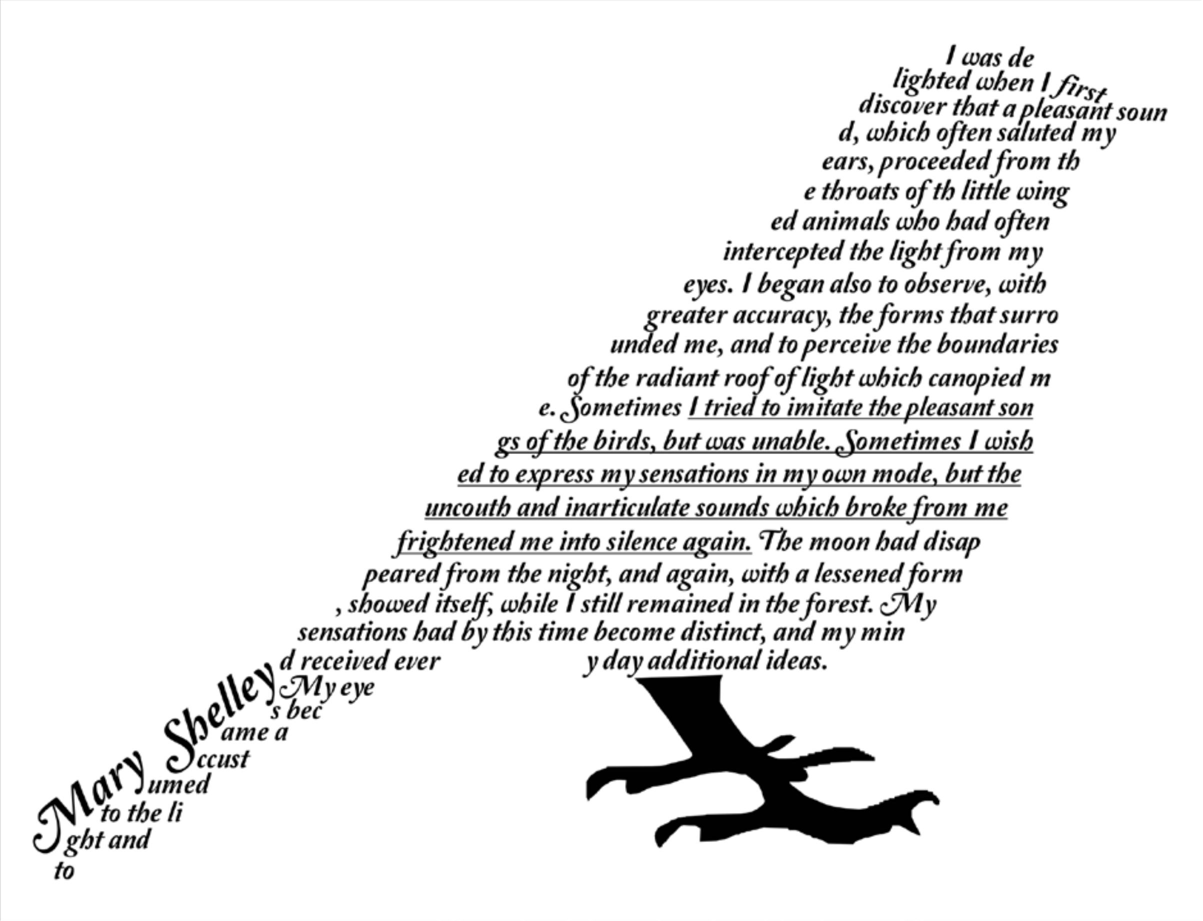
Chapter 4 - Study II: Brain structural correlates of foreign-language imitation[2]



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ORIGINAL ARTICLE

The Left, The Better: White-Matter Brain Integrity Predicts Foreign Language Imitation Ability

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Abstract

Speech imitation is crucial for language acquisition and second-language learning. Interestingly, large individual differences regarding the ability in imitating foreign-language sounds have been observed. The origin of this interindividual diversity remains unknown, although it might be partially explained by structural predispositions. Here we correlated white-matter structural properties of the arcuate fasciculus (AF) with the performance of 52 German-speakers in a Hindi sentence- and word-imitation task. First, a manual reconstruction was performed, permitting us to extract the mean values along the three branches of the AF. We found that a larger lateralization of the AF volume toward the left hemisphere predicted the performance of our participants in the imitation task. Second, an automatic reconstruction was carried out, allowing us to localize the specific region within the AF that exhibited the largest correlation with foreign language imitation. Results of this reconstruction also showed a left lateralization trend: greater fractional anisotropy values in the anterior half of the left AF correlated with the performance in the Hindi-imitation task. From the best of our knowledge, this is the first time that foreign language imitation aptitude is tested using a more ecological imitation task and correlated with DTI tractography, using both a manual and an automatic method.

Key words: speech imitation, arcuate fasciculus, DTI, lateralization, language learning

Speech and voice imitation require the transformation of acoustic information into motor responses (Canevari et al. 2013). A striking phenomenon in this topic is the large individual variability in foreign language pronunciation ability, from very talented individuals possessing excellent mimicking capacities to very poor imitators (Golestani and Pallier 2007; Reiterer et al. 2011; Hu et al. 2013). This variability might depend on underlying functional-neuroanatomical individual differences (Reiterer et al. 2011; for a review, see Zatorre 2013). The neural network involved in speech imitation abilities, mainly reported on the left hemisphere, includes the inferior frontal gyrus (IFG), the superior temporal gyrus (STG), the Heschl's gyrus, the supramarginal gyrus (Catani et al. 2005; Kappes et al. 2010; Adank, 2012), as well as the insular and premotor cortices (Berthier et al. 2012; Hu et al. 2013). All these regions are connected via the three segments of the arcuate fasciculus (AF: long frontotemporal segment, anterior parietofrontal segment, and posterior parietotemporal segment) or, following an alternative classification, via the long and posterior segments of the AF and the ventral superior longitudinal fasciculus (SLF-III, Fernández-Miranda et al. 2015; Wang et al. 2016). Interestingly, individual differences in other domains of language learning abilities have been already associated to microstructural variability in these pathways (Catani et al. 2007; López-Barroso et al. 2013; Ripollés et al. 2014).

Speech imitation has been defined as copying phonological parts of a linguistic stimulus (Kappes et al. 2010; Shuster et al. 2014), being an ability crucial for both language acquisition and second-language learning (Fitch 2010; Kappes et al. 2010; Shuster et al. 2014). Imitation tasks require the proper perception of the speech input-model and the ability to correctly produce a copy of that model, taking into account complex tonal features as well as subtle phonetic and contour changes (Jilka, 2009). When imitating speech materials from their native language, subjects focus overall on prosodic information (because the phonemic segmentation process in those languages has been already acquired). However, imitation of a completely new language—requiring accurate attention to the sounds and phonotactic structures that differ from the native language—involves phoneme-segmentation processes and relies on the ability to reproduce those new perceived sound patterns (Jilka 2009). Besides, there is an interesting phenomenon in which a speaker changes his/her own pronunciation to mimic a conversational partner, named “phonetic convergence” (also known as “chameleon effect”) (Dell and Jacobs 2016). This phenomenon involves the imitation of speech features of the model such as voice intensity, fundamental frequency (the particular sound-wave elicited by the vibrations of the vocal cords), temporal and spectral information to segment the speech stream into phonemes (extracted, e.g., from the “percussive” onsets and/or silences preceding the pronunciation of some consonants), and the specific gestures that the model speaker is performing to pronounce each word or phrase (Garnier et al. 2013; Binder 2016; Blumstein and Baum 2016; Leonard and Chang 2016). In the present study, the term “speech imitation” will be used in a broad sense that may include some traits from the “phonetic convergence” phenomenon, such as the copy of prosodic traits.

A largely discussed issue is the lateralization of language-related functions and neural structures. As Corballis (2010) proposed, the dominant left representation of language could be the consequence of a bias introduced by the incorporation of an articulatory-vocalization neural loop (left-lateralized even in nonhuman species; Aboitiz 2012), or the resultant way of dealing with the complexity of manual skill and language itself. In a similar way, hemispheric lateralization has been recently proposed as a special case of functional specialization, a process that decomposes large brain functions into smaller processes to reduce the functional interference and improve the efficiency of the system (Gotts et al. 2013). Although the final explanation remains open, left-lateralized activity and better integrity in the left AF have been previously reported as related to speech tasks (Parker et al. 2005; Menenti et al. 2011; Adank et al. 2013; Saygin et al. 2013; Ocklenburg et al. 2014; Sreedharan et al. 2015), phonological awareness and phonological memory (Yeatman et al. 2011). Furthermore, it has been proposed that the left auditory cortex extracts information from short temporal windows, which contributes, for example, to the processing about place of articulation during a speech stream (information regarding where in the oral cavity and in which manner phonemes are pronounced, Idsardi and Monahan 2016). Hence, the left auditory structures have been suggested to be more important for speech discrimination than their right homologues (Zatorre et al. 2002; Poeppel 2003). The right auditory cortex might be preferentially involved in decoding the frequency content of the speech signal (see Poeppel 2003; and Giraud et al. 2007), and it has been more related to pitch and tonal discrimination (Zatorre et al. 1992; Zatorre et al. 2007) as well as prosody (Friederici and Alter, 2004; Sammler et al. 2015). Interestingly, higher volume of grey- and white-matter (WM) in the left auditory cortex, and better WM microstructural organization in the left temporoparietal region and IFG seem to be predictive of the ability to learn new words and articulate foreign language sounds (Golestani and Pallier 2007; Zatorre 2013). Overall, these results point to the left dorsal network as a crucial pathway for language learning (Scott and Wise 2004; Rodríguez-Fornells et al. 2009), but the issue regarding the specific neural correlates of foreign language imitation remains open. Besides, the large variability that exists in the lateralization of WM pathways (Catani and Bambini 2014) could be related to the large variance observed in speech imitation processes (Catani et al. 2007).

Only a few attempts to investigate the functional or structural neural correlates of foreign language imitation aptitude have been carried out recently (Reiterer et al. 2011). Based on the previous literature commented above, a better white matter microstructural organization in the left hemisphere is expected to be strongly related to the speech-imitation performance (Poeppel 2003; Zatorre et al. 2007); however, prosodic cues may play a role (as in L1 or L2 imitation tasks) and thus partial involvement of the right hemisphere could be found as well (Sammler et al. 2015). In the present investigation, we aimed to study for the first time, to which extent morphological variability and lateralization degree in the AF could predict speech imitation aptitude. With that aim, we used a more ecological task to test foreign language imitation (using sentences and words from a nonexperienced language, instead of the syllables, sounds, or words paradigms previously applied). Besides, WM tractography analysis of the AF was conducted using two different approaches (i.e., a deterministic-manual one, and an automatic one that combines a deterministic approach with corrections and refinement of the tract based on a probabilistic atlas). The manual-deterministic approach allowed us to dissect the AF in different segments (López-Barroso et al. 2013) and extract the mean diffusivity values for each branch. The automatic method, on the other hand, is based on the hypothesis that WM can present variations in the diffusivity values along each single tract; these variations have been previously described for the AF and could be due to intrinsic variability or the geometry of the tract, among other factors (Klingberg et al. 2000; Yeatman et al. 2011). This approach allowed us to extract 100 diffusivity values along the AF and, thus, investigate in more detail whether there is a specific region in this pathway specially correlating with the imitation abilities of our participants.

Materials & Methods

Participants

Fifty-two native German-speakers (25 females; age range: 19–43 years, mean age 26.33 ± 5.38) participated in this study, who were recruited via two universities’ outreach (University of Tübingen and University of Stuttgart), community advertisements, and local media. All of them were students or young academics and reported no hearing (self-reported, verified by experimenter, but not audiometrically), neurological or psychiatric disorder. All participants reported to be right-handed, and all but two completed the Edinburgh handedness inventory (Oldfield 1971), which confirmed their right-handedness (group-mean score (n = 50) = 0.95 ± 0.096). None of them had previous experience or training in Hindustani-derived languages. Furthermore, information about previous speech and musical training was obtained via self-report (online questionnaires), such as the number of musical instruments played (mean: 1.04 ± 0.99), number of German dialects (mean: 1.58 ± 1.73), and number of foreign languages (mean: 2.57 ± 1.64) spoken. Moreover, participants also completed the AMMA test (Advanced Measures of Music Audiation, Gordon 1989) in a web-based version using head-phones (mean score: 58.96 ± 7.99). Participants received financial remuneration for their participation after giving informed written consent to participate in the study. The study was approved by the local Ethics Committee and was in accordance with Helsinki's declaration.

Behavioral Task

To characterize speech imitation aptitude, a behavioral language imitation task was carried out, consisting of *ad hoc* imitation of three polysyllabic (7–11 syllables) Hindi sentences and one trisyllabic Hindi word spoken by a model Hindi speaker (Reiterer et al. 2011). Hindi was selected to test "pure" imitation abilities as this was the first time that our participants were exposed and requested to imitate this language. Furthermore, we decided to use these stimuli, in which all natural levels of phonetics and prosody co-occur in time, because we were interested in the ability to imitate speech materials in a more ecological way, closer to a real-life situation. During the speech-imitation task, participants listened three times to each sentence (in a nonself-paced way) via Sennheiser headphones, and were instructed to imitate the sentence as accurately as they could immediately after the third time they listened to the stimuli. A pilot experiment showed that repetition after one listening trial was not feasible with unknown language stimuli. It was a direct imitation, without any practice or familiarization trials, and with no possibility to repair the response. We selected this simple task and instructions to capture an authentic and spontaneous first imitation of this new language. Speech production of each participant was recorded in a sound-proof room and later subjected to web-based native speaker judgements in India (30 raters, 15 females; age range: 20–55 years, mean age: 27.63 ± 6.6; inter-rater reliability, $r = 0.9$). The raters were naïve (no linguistic experts) and blind regarding the linguistic background of the participants and were instructed to score them based on their global impression of "sounding like a native Indian". The raters got financial remuneration, were recruited from our Indian cooperation partners (NCS, SR, VK) and came from different regions of India with Hindi as either their first or their second language (language backgrounds: Hindi (most raters), Bengali, Manipuri, Marathi, Telugu, Kannada). Most of the raters had a university or tertiary educational background (60%), only very few (around 20%) had linguistic expertise and none of them had explicit phonetic expertise. We deliberately chose to address naïve raters, because it is known from the literature (Bongaerts et al. 1995; Flege et al. 1995; Bongaerts 1999) and from prior research (Christiner and Reiterer 2013; Berken et al. 2015) that for the fields of speech and singing evaluation the performance of naïve raters is comparable to that of experts. To ensure that the raters understood their task correctly, we instructed them to think of characteristics such as word-stress, the rhythm of the language, intelligibility, and overall pronunciation. We used a Likert-based intuitive rating bar ranging from "10" to "0" (10 = maximum native-speaker-like, 0 = minimum native-speaker-like) and calculated the means of all sentences/all raters. To enhance evaluation quality, recordings from 18 Hindi native speakers were randomly inserted into the Internet database. Speech samples were presented in a random order (for more details, see Jilka 2009; Reiterer et al. 2011).

Imaging Acquisition and Analysis

Diffusion tensor imaging (DTI) and T_1-weigthed MDEFT (Modified Driven-Equilibrium Fourier Transform) data was obtained from a 1.5-T Siemens scanner (Erlangen, Germany). Diffusion tensor imaging parameters were: repetition time (TR) = 6700 ms, echo time (TE) = 82 ms; field-of-view (FOV) = 256 × 256 mm; matrix size = 128 × 128; slice thickness = 2.5 mm; no gap; 52 axial slices; voxel size was 2 × 2 × 2.5 mm. Diffusion was measured along 12 noncollinear directions, chosen according to Siemens DTI acquisition scheme using *a b* value of 800 s/mm^2, and including *a b* = 0 as the first volume of the acquisition (in addition to the other 12).

The T_1-weigthed image parameters were: TR = 7.92 ms; TE = 2.48 ms; inversion time (TI) = 910 ms; FOV = 176 × 256 × 256 mm; flip angle = 16°; voxel size = 1 × 1 × 1 mm; matrix = 256 × 256; 176 sagittal slices obtained with an eight-channel head coil.

Manual Reconstruction of DTI Tracts

To preprocess the diffusion-weighted images, first, the brain was virtually separated from the rest of the head using FSL's Brain Extractor Tool (Smith 2002; Smith et al. 2004; Woolrich et al. 2009). Afterward, motion and eddy-current correction was performed using FMRIB's Diffusion Toolbox, part of the FMRIB Software Library (FSL 5.0.1 www.fmrib.ox.ac.uk/fsl/). The *b*-vectors gradient matrix was then rotated to take into account the corrections made at the previous stage, by using the fdt_rotate_bvecs software included in the FMRIB Software Library. The diffusion tensors were then reconstructed using Diffusion Toolkit's least-square estimation algorithm for each voxel, and Fractional Anisotropy (FA) was calculated (Ruopeng Wang, Van J. Wedeen, Martinos Center for Biomedical Imaging, Massachusetts General Hospital, www.trackvis.org).

Whole-brain deterministic tractography was performed in Diffusion Toolkit, using an interpolated streamlines algorithm, with a maximum curvature threshold of 35 degrees and a minimum FA threshold of 0.2. The fiber direction is assumed to correspond to the principal eigenvector (the eigenvector with the largest eigenvalue). This vector was color-coded (green for anterior–posterior, blue for superior–inferior, and red for left–right directions) to generate a color-coded FA map.

Dissections were carried out for each subject in the native space and in both hemispheres. The three segments of the AF were dissected on Trackvis software using three main manually defined regions of interest (ROIs) as described in previous studies (Catani et al. 2005, 2007; López-Barroso et al. 2013). The ROIs were defined on the FA and FA color-coded maps according to individual anatomical landmarks, instead of atlas-based constraints that neglect individual differences (López-Barroso et al. 2013). Specifically, a first ROI was delineated in the coronal view, anterior to the central sulcus, encompassing the fibers going to the IFG (including Broca's area; Brodmann's areas 44 and 45). Then, in the axial slice a second ROI was depicted covering the WM underlying the medial temporal gyrus (embracing the fibers traveling to Wernicke's territory; Brodmann's areas 22p, 41, and 42). Finally, a third ROI was drawn on the sagittal view, covering supramarginal and angular gyri and encompassing the fibers traveling to Geschwind's territory (Brodmann's areas 39 and 40). These ROIs were combined to encompass the three rami of the AF: the long (between IFG-Broca's and Wernicke's areas), the anterior (linking IFG-Broca's and Geschwind's territories), and the posterior (uniting Wernicke's and Geschwind's territories) segments. Artefactual fibers were removed using exclusion ROIs.

We restricted our statistical analysis to FA and volume measures based on recent investigations that showed these WM parameters to be very sensitive to individual differences (Saygin et al. 2013; Ocklenburg et al. 2014; Sreedharan et al. 2015). We extracted the volume and the FA from each of the three segments of the bilateral AF, and the sum of the three segments of each hemisphere to obtain the values for Complete Left and Complete Right AF. A lateralization index was calculated for each parameter and segment [Lateralization Index = (values on the L − values on the R) / (values on the L + values on the R)] and included in the analysis to see whether the WM organization had a clear hemispheric preference in relation to imitation abilities. The lateralization index ranges from −1 to 1: negative values represent right lateralization, values around zero symmetrical distribution, and positive values left lateralization (López-Barroso et al. 2013). Pearson correlation between all these measurements and the Hindi-imitation score was performed. Significance of all the reported results was thresholded at a $P < 0.05$ corrected for multiple comparisons by means of False Discovery Rate (FDR), to control for the proportion of false positives relative to true positives (Benjamini and Hochberg 1995).

Automatic Reconstruction of the Tracts

Variations in diffusivity values along each single WM tract, and specifically for the AF, have been previously described (Yeatman et al. 2011). These variations may be explained by (i) intrinsic variability of the tract, (ii) the geometry of the tract, and (iii) neighboring tracts (i.e., partial voluming due to crossing fibers problems) (Klingberg et al. 2000; Yeatman et al. 2011). Since a tract may possess different values of diffusivity in its trajectory, certain region(s) may show a stronger correlation with a given behavioral variable than the rest of the portions of the tract. Hence, to look for the exact portion of the AF which may be specifically involved in foreign language imitation abilities, we used another approach applying an open-source software for automated fiber-tract quantification (AFQ, Stanford University, described in Yeatman et al. 2012). AFQ automatically identifies major fiber tracts and quantifies WM properties along their trajectories. To apply the AFQ pipeline to our data, we first coregistered the brain extracted DTI raw-volumes and a T_1 image of each subject (with the b_0 as reference), realigning them to the AC–PC line afterwards (anterior commissure, posterior commissure). Then, we performed some preprocessing steps using mrDiffusion and specifically, dtiInit pipeline (VistaLab, Stanford University) on these images: b-vectors were rotated, eddy current correction was performed, DTI volumes and T_1-structural images were aligned, b-vectors were reoriented and aligned, and diffusion tensors were reconstructed using the simple least square fit. Finally, a file containing all the fiber and tensor information that the AFQ requires was built (a file called dt6).

Once the preprocessing was done, AFQ was applied in each subject, performing (i) a whole-brain tractography, (ii) the segmentation of 20 main fascicles (based on the Wakana et al. 2007 white-matter atlas, see Yeatman et al. 2012) using a 2-ROI approach and comparing and refining it by comparing each fiber in each fascicle with a probabilistic fiber tract atlas, (iii) a cleaning of outlier-fibers that deviate from the core of each fiber-group (the core of each tract is defined by creating a 3D Gaussian, removing afterwards those fibers importantly deviating from the center), followed by (iv) the calculation of diffusion measurements in 100 nodes along the trajectory of each fiber group, weighting each fiber's contribution to the measurement based on its distance from the tract core. Although within these measurements there is a value for volume of the tract, the authors of the original paper (Yeatman et al. 2012) strongly suggest not to take this parameter into account for analysis since it is considered a noisy and imperfect measure. Due to this fact, we decided to restrict the analysis to FA values. It is important to note that, since all the dissections are performed using a 2-ROI approach, in the specific case of the AF this means that the tract reconstructed corresponds only to the long segment in the manual-deterministic dissection (i.e., any measurement is restricted to the pathway linking inferior frontal and superior temporal regions, without taking into account the indirect segments that create a structural communication with the supramarginal and angular gyri).

Taking the FA measurements calculated for each node along the AF by the AFQ software, we calculated and extracted a lateralization index (in the same way than for the manually dissected data) for each node. Pearson correlations between the Hindi-imitation score and (i) the FA in each node on the one hand, and (ii) the lateralization index of FA in each node on the other hand were performed. For each correlation, the AFQ function for Multiple Comparisons was used to check for a FWE corrected P-value < 0.05 at the individual nodes and at a cluster level (this AFQ function returns, among other values, the minimum number of sequential nodes above the alpha threshold to consider that that particular group of nodes is corrected for multiple comparisons at the cluster level).

Comparison Between Manual and Automatic Reconstructions

In addition, we were interested in performing a comparison between the manually and the AFQ dissected data and results. Hence, since the AFQ dissection limits the reconstruction to the long segment, a Pearson correlation between the mean FA values extracted for the long segment manually reconstructed and the mean of the 100 FA values calculated for the nodes obtained with AFQ was carried out.

Results

Behavioral Results

The Hindi-imitation task was extremely difficult: none of the participants ranged within the "native speaker" range in which the 18 inserted Hindi-native speakers' samples were scored (mean = 9.50 ± 0.60; range = 8.07–9.90 points), although none of them was at the lowest end of the scoring scale either (<2). The mean Hindi score for the full sample was 4.84 ± 1.11 (range = 2.65–7.74 points).

To control the influence of the musical and language experience of our subjects on the Hindi-imitation task, a Pearson correlation with the Hindi-imitation score was performed, but no significant result was obtained for number of instruments ($r = 0.251$, $P = 0.073$), AMMA test ($r = 0.238$, $P = 0.096$), number of German dialects ($r = 0.208$, $P = 0.140$), or foreign languages ($r = 0.081$, $P = 0.570$) spoken.

Manual DTI Dissections: Correlations with Hindi-Imitation Score

Within the Right AF, a significant negative correlation between the Hindi-imitation score and the volume of the Complete AF was found ($r = -0.395$, $P < 0.005$, FDR corrected: see Fig. 1A and Table 1), meaning that the smaller the volume of the Right AF, the better the performance in the Hindi sentence-imitation task. No significant correlations were found for the left AF, neither for the long, anterior, or posterior segments, nor for the Complete AF, at a FDR-corrected $P < 0.05$.

We found a significant positive correlation between the Hindi-imitation score and the lateralization index for Complete AF volume ($r = 0.434$, $P < 0.005$, FDR corrected: see Fig. 1B and Table 1): the higher the lateralization of AF's volume to the left, the better the performance in the sentence-imitation task. See Figure 2 for some examples of the AF reconstructions and differences in lateralization across the best and worst participants.

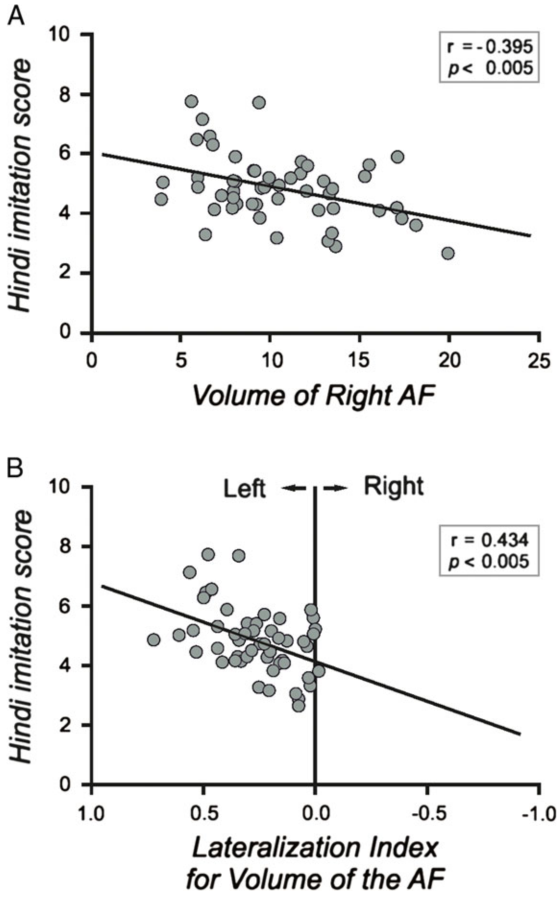

Figure 1. Relationship between DTI properties extracted from the manual reconstruction and performance in the Hindi-imitation task. Scatterplots show the Pearson correlation between AF volume and the Hindi-imitation score. (A) Negative correlation with the volume of the complete right AF. (B) Positive correlation with the lateralization index for volume of the complete AF. Lateralization index: values closer to 1 mean lateralization to the left, values around 0 represent symmetrical distribution, values closer to −1 mean lateralization to the right. These results evidence that the more lateralized to the left is the integrity of the AF, the better is the imitation of Hindi. Correlation index and P-values are displayed. Abbreviations: AF, Arcuate Fasciculus; DTI, Diffusion Tensor Imaging.

Automatic DTI Dissections: Correlations with Hindi-Imitation Score

After applying the multiple comparisons function to the automatically dissected data, taking into account the individual 200 nodes conforming the left and the right AF, we found a significant area in the anterior half of the left tract that correlated significantly with the Hindi-imitation score (see Fig. 3A). As depicted in Figure 3B (black line), this significant area (FWE-corrected at cluster level) was formed by 21 contiguous nodes (the minimum number of nodes considered as corrected given by the Multiple Comparisons function was 18); specifically, it contained nodes 23–43 (both included). No significant nodes or clusters were found for the right AF (see magenta line in the graph in Fig. 3B). Furthermore, no significant results were found either for the correlation between the Hindi-imitation score and the lateralization index calculated for the FA values in each node.

Comparing the Manual and the Automatic Reconstructions

As shown in Figure 3C, a significant correlation was found between the FA values extracted from the manually dissected left long segment and the mean of the 100 FA values calculated for the nodes obtained with AFQ for the left AF ($r = 0.762$, $P < 0.001$). In Figure 3D, four examples of the overlap between manual (in red) and automatic (in green) reconstruction can be observed.

Table 1 Details of the correlations between DTI parameters extracted from the manual dissection and the Hindi-imitation score (means, standard deviation, and P values displayed)

DTI parameters	Group mean (SD)	r (Pearson)	P value
FA L long segment	0.48 (0.02)	0.282	0.430
Volume L long segment	8.78 (3.14)	0.157	0.267
FA L anterior segment	0.41 (0.14)	0.142	0.316
Volume L anterior segment	3.50 (2.24)	0.040	0.776
FA L posterior segment	0.45 (0.02)	−0.069	0.629
Volume L posterior segment	5.30 (1.79)	−0.048	0.737
FA L complete AF	1.34 (0.15)	0.160	0.256
Volume L complete AF	17.57 (4.44)	0.112	0.429
FA R long segment	0.32 (0.24)	−0.015	0.918
Volume R long segment	3.10 (3.23)	−0.204	0.147
FA R anterior segment	0.46 (0.03)	−0.056	0.695
Volume R anterior segment	3.91 (1.95)	−0.271	0.052
FA R posterior segment	0.45 (0.02)	0.096	0.497
Volume R posterior segment	3.42 (1.26)	−0.253	0.069
FA R complete AF	1.23 (0.24)	−0.012	0.935
Volume R complete AF[a]	10.43 (3.82)	**−0.395**	**0.004**
Lat Index for FA of complete AF	0.05 (0.11)	0.105	0.460
Lat. Index for volume of complete AF[a]	0.26 (0.18)	**0.434**	**0.001**
Other variables of interest			
Number of musical instruments	1.04 (0.99)	0.251	0.073
Gordon AMMA test	58.96 (7.99)	0.238	0.096
Number of foreign languages	2.57 (1.64)	0.081	0.570
Number of German dialects	1.58 (1.73)	0.208	0.140

Notes: Abbreviations: DTI, diffusion tensor imaging; SD, standard deviation; FA, fractional anisotropy; L, left; R, right; AF, arcuate fasciculus; Lat. Index, lateralization index; AMMA, Advanced Measures of Music Audiation.

[a] Significant correlations with Hindi-sentence imitation score, at a $P < 0.05$ corrected for multiple comparisons by means of False Discovery Rate (FDR).

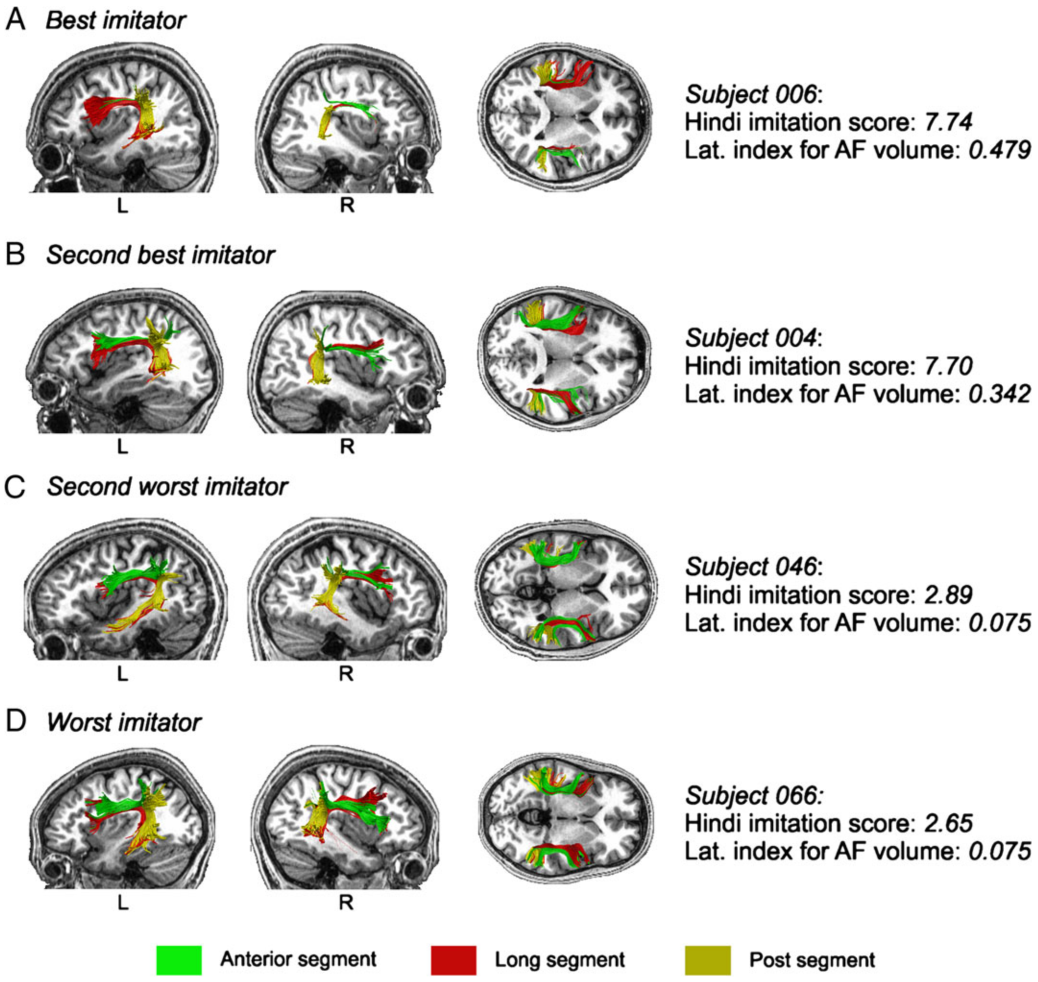

Figure 2. Examples of the manual AF reconstruction. Examples of AF reconstruction superimposed on the corresponding T_1 image of: (*A*) the most talented subject, (*B*) the second most talented subject, (*C*) the second less talented subject, and (*D*) the less talented subject. Individual Hindi-imitation scores and Lateralization indexes of the whole AF volume are displayed. The closer is the lateralization index to 1, the more lateralized is the AF volume to the left. Abbreviations: AF, Arcuate Fasciculus; Lat Index, Lateralization index.

Discussion

In this study, a manual deterministic and an automatic (combining a deterministic approach with corrections based on a probabilistic atlas) tractography analyses of the AF were performed to investigate the relationship between foreign language imitation aptitude and the WM organization of this tract. On the one hand, we manually dissected the left and right AF (distinguishing three rami: long, anterior—or SLF-III—and posterior; Catani et al. 2005; Fernández-Miranda et al. 2015; Wang et al. 2016) in 52 native-German speakers who completed a Hindi sentence- and word-imitation task rated by Hindi native speakers. On the other hand, the same DTI data was fed into the open-source AFQ software to obtain an automatic dissection of the right and left AF, from which WM measurements were extracted from 100 nodes along the tracts. This method allowed a more fine-grained analysis of which region within the AF tract correlated most importantly with foreign language imitation scores. Our results showed that larger lateralization of the overall AF volume to the left, as well as better WM microstructural organization (FA) in the anterior portion of the left long segment of the AF, predicted better performance in the Hindi sentence- and word-imitation task.

Imitation tasks require the correct perception of the input model and the ability to correctly reproduce the representation of that model (Jilka 2009). To imitate speech materials from their native tongue subjects focus mainly on prosodic patterns that they can understand and mimic, whereas imitation of a not-experienced language (i.e., Hindi in our case) requires a perceptive focus on the sounds and phonotactic structures that are not present in the native language, and the ability to articulate and pronounce the acoustic patterns as they have been perceived (Jilka 2009). Our more realistic task using a complete new language may request the reproduction of phonemes, as well as the copy of other characteristics such as the vocal intensity, the fundamental frequency, and some prosodic traits that may have helped participants to pronounce the speech-stream as the model speaker does. It is important to note the difficulty of our task: (i) the stimuli were sentences (which are long and more complex streams than single phonemes or words) and the exposure was limited to only three repetitions for each one; (ii) the language selected (Hindi) was completely new to our participants; and (iii) importantly, Hindi language contains phonemes that are uncommon across the languages of the world, making them difficult to perceive during the first exposures for listener of languages without these sounds

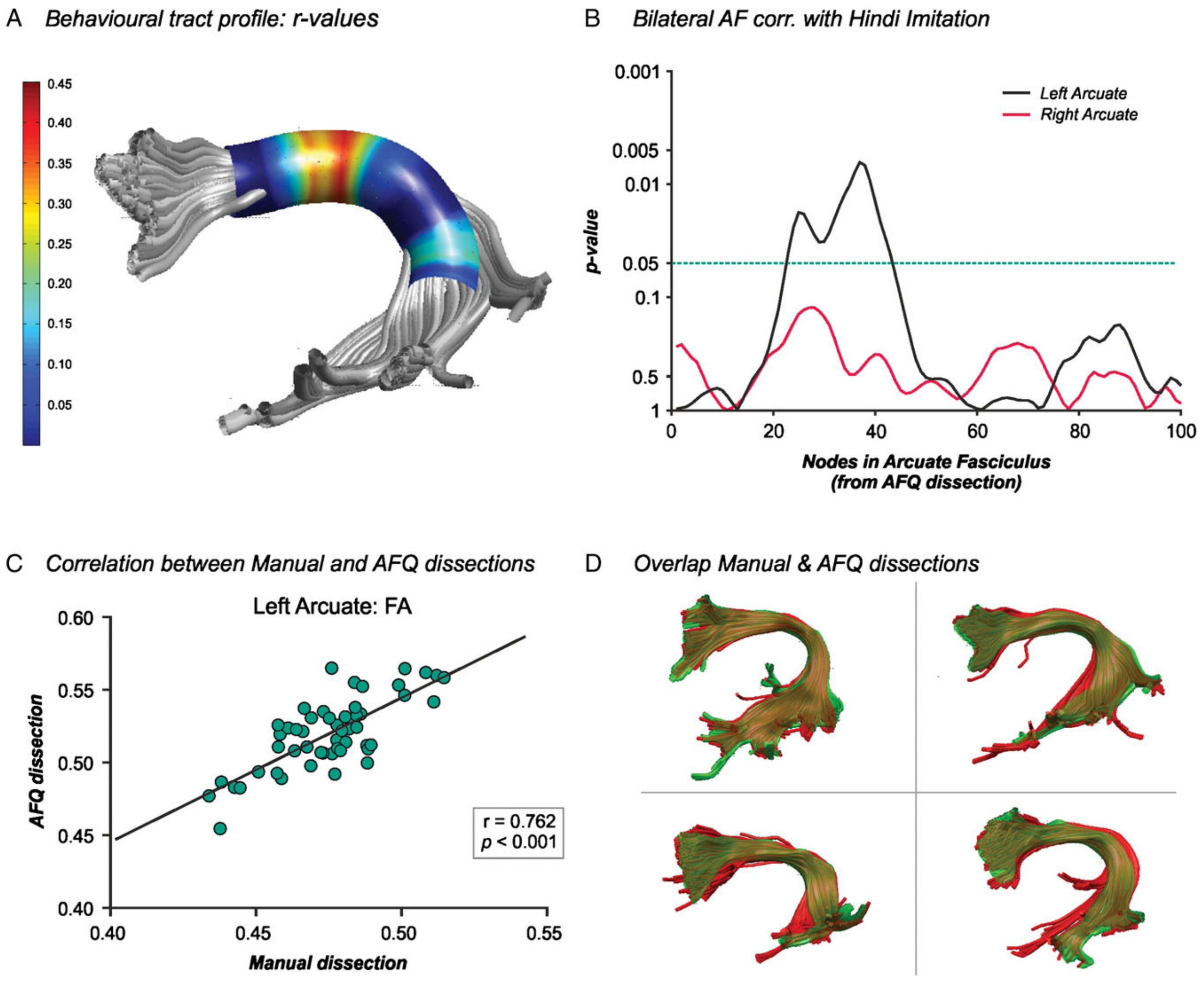

Figure 3. Results from the automatic fiber quantification analysis and the comparison with the manual reconstruction. (*A*) Correlation between Hindi-imitation score and the values of FA in the 100 nodes of left AF: *r*-values are projected on the left AF of one of our subjects, warm colors show the significant cluster between node 23 and node 43. (*B*) Graph showing the correlation between Hindi-imitation score and the FA values along the 100 nodes for the left AF (black line) and the right AF (magenta line); the green line represents the alpha threshold from which FWE corrected (at cluster-level) results are found. (*C*) Correlation between mean FA value for the left long segment extracted manually and the mean FA values from the 100 nodes reconstructed with AFQ for the left AF, in the 52 subjects. (*D*) Visual overlap between manual (in red-transparent) and automatic (in solid green) reconstruction of the left long segment—AF (4 different subjects shown as examples).

(Golestani and Zatorre 2004; Ventura-Campos et al. 2013). Furthermore, the task was purposely chosen to be as difficult as possible (few stimuli, little exposure) to elicit individual differences and to avoid a ceiling effect. Despite these difficult aspects, imitation was possible for all the participants: no one got the lowest score (between 0 and 2), and some participants even obtained moderately high scores (around 7). Besides, a previous investigation using the same task (Reiterer et al. 2011) reported a normal distribution for Hindi-imitation ability, which is in agreement with the Gaussian distribution that language aptitude has been described to adopt (Selinker 1972; Wells 1985).

The left bias in the lateralization of the AF in relation to foreign language imitation found by two different methods in the present study is in convergence with the predominant view that the left auditory cortex is more predisposed to process language stimuli than its right-hemisphere homologue (Zatorre et al. 2002; Poeppel 2003; Friederici and Alter 2004; Giraud et al. 2007). It has been proposed that, during auditory perception, the left auditory areas extract information from rapid changes in timing and contour variables along the auditory stream. Such changes in the specific case of speech give the listener cues about the place of articulation; in other words, information about how the speaker is pronouncing the different phonemes (Poeppel 2003). Furthermore, previous reports have described two different types of listeners: (i) the fundamental listeners, who mainly decode the keynote or fundamental pitch of the stimuli and (ii) the spectral listeners, who focus on the lowest harmonic components of the sound signal (which nevertheless allow them to perceive the speech contour) (Schneider et al. 2005a, 2005b; Postma-Nilsenová and Postma 2013). Interestingly, Schneider and collaborators (2005a, 2005b) reported that fundamental listeners rely more on the left temporal cortex (i.e., present more GM and enhanced functional magnetoencephalography activity on the left Heschl's gyrus), while spectral listeners depend more on the right auditory cortex. Thus, although it is speculative at this point, this may suggest that the left-lateralized results found in this study could be partially explained by a greater number of fundamental listeners among our participants.

Speech and voice imitation tasks require the existence of an auditory-to-motor mapping process in which the AF might be helping, allowing the repetition of phonological elements (Canevari et al. 2013) and perhaps other acoustic characteristics (such as prosodic patterns, Sammler et al. 2015). We hypothesized that our participants might have increased their attention to the articulatory information to transform the auditory input into the required motor patterns. Thus, participants might rely on fast feedforward/feedback auditory-(pre)motor loops that calibrate the articulatory representations of the new phonological sequences, recruiting the AF as well as attentional and phonetic-working memory networks (Cunillera et al. 2009; Rauschecker and Scott 2009; Rodríguez-Fornells et al. 2009; López-Barroso et al. 2013, 2015). In line with this idea, Zatorre and colleagues (1992) described that during phonetic judgement (i.e., discriminating final consonants between syllables) it is necessary to recruit neural circuits able to access articulatory representations, such as left IFG/BA6 and surrounding regions. The IFG and premotor cortices might transmit information on programmed articulatory sequences about to occur (feedforward) into the auditory and inferior parietal regions, which in parallel receive information about ongoing pronunciation (feedback) (Rauschecker 2012). This information would be compared with the auditory templates stored from previous exposures to the foreign language in the posterior STG (Warren et al. 2005). The template-matching algorithm might allow the detection of coincidences between the stored “phonological templates” and the new input (Warren et al. 2005), permitting the calibration and minimization of ongoing production errors (Rauschecker and Scott 2009), with the IFG and premotor regions acting as a top-down mechanism regulating this process.

In agreement with this idea, Foreign Accent Syndrome studies have highlighted the importance of certain structures involved also in speech monitoring and cognitive control (i.e., anterior insula, deep frontal operculum, anterior cingulate cortex) that may be important for pronunciation and foreign language imitation (Moreno-Torres et al. 2013). Similarly, several studies have shown that difficult speech processing relies on cortical regions in which comprehension and production overlap (Adank 2012). Specifically, vocal control and speech production have been described to involve the anterior cingulate area, supplementary motor area, basal ganglia (mainly the ventrolateral thalamus and the putamen), and the anterior insula for the initiation and sequencing of speech (Jürgens 2002; Guenther 2006). In addition, to carry out the sound production (perceiving the output and making corrections based on the auditory and proprioceptive feedback), it is necessary to activate the face area of the motor cortex (precentral gyrus, including Broca’s region and the deep frontal operculum), the somatosensory cortex, the primary auditory cortex and the auditory association cortices (i.e., superior and middle temporal gyri), and the inferior parietal cortex (Jürgens 2002; Brown et al. 2006; Guenther 2006; Kleber et al. 2013; Zarate 2013).

In addition to these neural networks involved in the control of vocalization and speech production, previous fMRI studies have described a close relationship between functional activation and connectivity across the mentioned areas and language learning abilities. Specifically, Ventura-Campos and colleagues (2013) observed activations in the bilateral inferior frontal operculum/anterior insula, the bilateral STG, and the right middle frontal gyrus during a foreign-language phoneme identification task. After 2-week training in this phoneme identification paradigm, some other regions were added, such as the inferior parietal lobe bilaterally, bilateral caudate head, and right cingulate gyrus. The BOLD response in the left frontal operculum after training correlated positively with behavioral improvement in the discrimination task (Ventura-Campos et al. 2013). Furthermore, the talent for imitating words, sentences, and a text in English and Hindi/Tamil was previously found to be associated with the activation in the left perisylvian network, including the premotor cortex and the inferior parietal lobe (Reiterer et al. 2011). Performance in a word-learning task has also been previously found significantly correlated both with the microstructure of the left long segment of the AF and with the strength of the functional connectivity between left temporal regions (Wernicke’s area) and left inferior frontal areas (Broca’s territory, frontal operculum) (López-Barroso et al. 2013).

As these previous studies suggested (Reiterer et al. 2011; López-Barroso et al. 2013; Ventura-Campos et al. 2013), brain activity measured during in-scanner tasks or via resting-state functional connectivity parameters may be related to actual anatomical WM pathways. As a matter of fact, the AF is interconnecting these cortical regions: the inferior frontal region (with terminations that may arrive to pars opercularis, pars triangularis, ventral precentral gyrus, and the caudal part of the middle frontal gyrus), the inferior parietal lobe/supramarginal region, as well as primary and association auditory regions (which may involve STG, rostral and caudal middle temporal gyrus, and caudal inferior temporal gyrus) (Fernández-Miranda et al. 2015). Thus, the proper functioning of this auditory-motor system in foreign language imitation and learning might depend on the WM integrity and asymmetry of the AF, which, as proposed recently, has a general function in sensorimotor integration and control (Berthier et al. 2012; Rauschecker 2012).

This auditory-motor network has also been related to mirroring and production of informative actions, being a crucial system for social communication through the development of mimicking abilities (Catani and Bambini 2014). Evolutionarily, the expansion of auditory-motor connections through the AF (whose complexity increases along the phylogenetic scale) permitted humans to develop a system for auditory working memory critical for learning and imitating complex phonological sequences produced by conspecifics (Aboitiz 2012; López-Barroso et al. 2013). Ontogenetically, Perani and colleagues (2011) observed in newborns a WM connection between auditory cortex and premotor areas, but not the direct pathway connecting auditory cortex with IFG (Perani et al. 2011). Thus, the direct segment of the AF develops later during infancy compared with other WM tracts (such as the anterior segment of the AF, the inferior longitudinal fasciculus, or the frontal aslant tract), and its maturation has been described to continue until the age of 7 (Catani and Bambini 2014; Friederici 2015). Regarding the left-lateralization of language abilities, a cerebral dominance for vocalizations might originate from complex sequential motor patterns that could be more efficiently processed asymmetrically (Aboitiz 2012). Moreover, left lateralized activity during speech production (Menenti et al. 2011; Adank et al. 2013), greater left AF volume in relation to speech tasks (Parker et al. 2005; Saygin et al. 2013; Ocklenburg et al. 2014; Sreedharan et al. 2015), and better left AF microstructure related to phonological awareness and phonological memory (Yeatman et al. 2011) were previously reported. These ideas are in line with the widely extended view commented before, which assigns a particular acoustic preference to each hemisphere: left temporal areas more prompted to process rapid temporal variations that have been associated with language stimuli (as the voice-onsets and silences preceding the pronunciation of some consonants); right temporal areas more related to the processing of spectral changes, such as melodic contour and prosody (Zatorre et al. 1992, 2002; Poeppel 2003; Friederici and Alter 2004; Giraud et al. 2007; Sammler et al. 2015). However, this theory is still under debate since speech stimuli also depend on spectral features and the left-hemisphere dominance for "temporal" processing has not been unambiguously proved, while the right-hemisphere preference for spectral processing seems to be quite consistent in the literature (McGettigan and Scott 2012). Hence, McGettigan and Scott (2012) proposed that the real asymmetry might consist in the right auditory cortex possessing genuine preferences for specific properties of the acoustic signal, while the left hemisphere could not show any preference at all. Another interesting view was recently proposed by Gotts and collaborators (2013). These authors observed that the left hemisphere shows a greater preference for cortico-cortical interactions that are constrained toward the left hemisphere, while the right hemisphere presents more bilateral, interhemispheric interactions (Gotts et al. 2013). These authors also observed a correlation between vocabulary scores and intrahemispheric functional connectivity in language- and communication-related areas, such as the IFG, posterior and middle superior temporal regions, medial frontal areas, and the fusiform gyrus. These results suggest that speech production and comprehension (functions that request fast sequential interactions) may be better represented in the left hemisphere since they may benefit from shorter synaptic delays granted by the described preferential intrahemispheric processing (Gotts et al. 2013).

Despite this open debate, our results highlight a clear relationship between the WM microstructural organization of the AF and speech imitation aptitude, with a left-lateralization bias. In aphasia research, it has been suggested that the existence of a well-structured AF, as well as preserved cortical language-related areas on the left hemisphere, might be predictive of a better language recovery (Fridriksson 2010; Marchina et al. 2011; but see also Forkel et al. 2014). Interestingly, in infant language-learning research, Bishop and coworkers (Bishop 2013; Bishop et al. 2014) have suggested that the amount of left-lateralization might depend on the learning of language skills, evolving as language competence improves. Although there is controversy regarding the need of a specific lateralization for language functions (Dyukova et al. 2010; Fridriksson 2010), a left-bias in the integrity of language-related pathways has frequently been described and reported as crucial for foreign language imitation and learning (López-Barroso et al. 2013; for a review, see Zatorre 2013).

Regardless of the lateralization, an interesting point to discuss is that our results from the manual dissection are found only for the complete AF volume (no significant results were found for the three branches separately), while the results from the automatic reconstruction are restricted to the long segment. Different roles in speech repetition for the different segments of the AF were previously suggested (Catani et al. 2005; Dick and Tremblay 2012), as well as their diverse involvement in language and nonlanguage processing (Berthier et al. 2012), but their specific functions are still under discussion. We hypothesized that the present task might have required the contribution of all three AF segments as a whole, due to its complexity (perceive and reproduce phonetic and some frequency- or contour-related characteristic of the stimuli) and novelty. Actually, looking at the manually dissected results it seems the case that speech imitation might rely on the three branches of the AF (dorsal stream) to ensure communication between all the components of the auditory-perceptive, auditory-working-memory, and oromotor loop (Rauschecker 2012), which might have a crucial role for storage and learning of novel words, and thus, a new language (Schulze et al. 2012). However, when looking at specific differences inside the tract with the automatic method, the long segment seems to possess more weight than the indirect rami. In any case, future research might shed light on the specific functions of the three branches of the AF and their relative importance in speech perception and production.

The present investigation may comprise some limitations, mainly associated not only with the DTI tractography analyses selected but also with the resolution of the images acquired here. One of the most common systematic errors in the DTI modeling process is the inadequacy of the tensor model to characterize fiber orientation when there is more than one fiber population within a voxel, and in which the Gaussian tensor model assumes the principal eigenvector as the only fiber orientation in the voxel (Jones 2008). This has been called the "crossing fiber issue" and although some solutions have been described and applied in the last years to overcome it, these new methods (i.e., spherical harmonic decomposition, Q-ball imaging, etc.) usually need more processing time and higher resolution images than the ones obtained for the present study (Jones 2008; Salat et al. 2009; Seunarine and Alexander 2009). As a matter of fact, the resolution of the images acquired for the present study may have prevented us from finding distinct results depending on the different segments (in the manual reconstruction) and/or to observe a more homogeneous pattern of diffusivity values along the whole long segment (in the case of the automatic method). Regarding the automatic reconstruction using AFQ, although this method may be remarkably interesting for localizing specific regions within a fiber tract in which some plastic or predisposing effects can be particularly strong and that may be lost when looking only at the tract-mean, as the creators of the method sustain, one should consider that an automatic method could never adapt to large interindividual differences. Moreover, in the particular case of the present study, we have focused in the AF, a tract that shows large important variability among individuals (Catani et al. 2007) and for which the AFQ program presents some problems in reconstructing the right-hemisphere pathway (Yeatman et al. 2011). However, as shown in Figure 3C,D, it is important to note the high correlation found between the FA values for the left AF extracted both manually and automatically ($r = 0.762$, $P < 0.001$), and how well the outputs from both types of reconstruction match (visually).

Conclusion

To conclude, based on previous reports (Catani et al. 2005; Berthier et al. 2012; López-Barroso et al. 2013; Zatorre 2013; Sreedharan et al. 2015) and our present results from both manual and automatic dissections, it emerges that the crucial characteristic underlying foreign language imitation skills is the integrity of the WM pathways whose function is the translation and mapping of perceived sounds into speech production. Furthermore, it seems that the direct pathway of the AF is the most crucial for these functions and capacities, especially a region in the anterior half of the left long segment. To the best of our knowledge, this is the first time in which imitation abilities are directly related to DTI tractography results, based on two types of dissection approaches, and showing a clear relationship between the lateralization of the AF and individual differences in speech imitation/pronunciation aptitude.

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Notes

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Chapter 5 - Study III: White matter structure predicts music skills in non-musicians[3]

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[3] This work corresponds to:

Vaquero, L., Penhune, V., Escobar-Ramos, N., Cucurell, D., François, C. & Rodríguez-Fornells, A. "White-matter structural connectivity predicts fast music learning in non-musicians" (Working Paper).

Abstract

Music learning has received increasing attention in the last decade due to the variety of functions involved during its practice, as well as to the benefits that have been reported to be elicited by long-term music practice (via brain plasticity mechanisms). In the present investigation we collected white-matter structural MRI data from healthy individuals without musical background. Using deterministic tractography, we dissected the corticospinal tract (CST) and arcuate fasciculus (AF) bilaterally. After the MRI-scan session, participants assisted to a behavioural session in which they completed a rhythm synchronization task and a piano-melody learning task. We found that volume in the right CST predicted the initial performance in the rhythm task, while microstructural organization of the AF predicted the synchronization improvement during the rhythm-synchronization task as well as the learning speed during the melodic learning. These results confirm the important role of white-matter microstructural connectivity in supporting future learning processes (structure-function coupling reported in individual differences research). In the present work, the morphology of CST and AF pathways showed a close relationship with the strong variability observed in music learning, as it was previously suggested in research comparing professional musicians and non-musicians.

5.1 Introduction

Music learning is a highly demanding and motivating activity, that engages a wide variety of neural functions (from pure perception to modulation of emotions, Jäncke, 2009; Koelsch, 2010). Learning to play a musical instrument has been reported to elicit brain plastic modifications, at both the structural and functional level (Jäncke, 2009; Münte et al., 2002). Specifically, structural modifications are reported in regions engaged during music practice such as the primary auditory cortices (Koelsch, 2010; Schneider et al., 2005a,b), primary somatosensory and motor cortices (Bermudez et al., 2009; James et al., 2014), premotor and supplementary motor regions (Chen et al., 2012, Herholz et al., 2015), and limbic areas (Koelsch, 2010; Strange et al., 2014). Functionally, musical training improves motor synchronization, motor reaction times and auditory discrimination abilities (Bailey et al., 2012, 2014; Zatorre et al., 2007). Interestingly, the improvement induced by musical training is not restricted to the musical domain but can transfer to other cognitive functions such as: speech processing, working memory, attention, general intelligence or phonological awareness (Besson et al., 2011; Moreno & Bidelman, 2014; Patel, 2011).

Previous research focusing on other cognitive and auditory-motor activities shows a large inter-individual variability associated to music performance and learning (Engel et al., 2014; Herholz et al., 2012; Herholz et al., 2015; see also Vaquero et al., 2016 for language imitation abilities). These individual differences could be partly explained by genetic and epigenetic contributions, in the sense that some individuals might develop more efficiency in those cognitive processes underlying music learning. At the same time, the neuroplasticity mechanisms induced by lifetime experiences with the environment can also explain the inter-individual variability observed in music learning performance (Zatorre, 2013). Recent human magnetic resonance imaging (MRI) research using voxel-based morphometry or DTI techniques has shown that inter-individual variability in several cognitive functions can be predicted by the local structure of grey (GM) and white (WM) matter (Càmara et al., 2010; Kanai & Rees, 2011; some examples in music: Imfeld et al., 2009; Steele et al., 2013; James et al., 2014; for a review see Zatorre, 2013), highlighting the important coupling between brain structure and cognitive functions.

Most of the studies in the field of music neuroscience have used cross-sectional designs comparing expert musicians to non-musicians and claim that the differences between groups are, most likely induced by the massive and complex training carried out by the musicians (Jäncke, 2009; Patel, 2014; for the same conclusion in longitudinal studies, see review by Besson et al., 2011). However, brain differences could be already present at the beginning of this specific training and hence, may reflect predisposing factors that may influence the learning outcome instead of neuroplastic consequences of an intensive and sustained practice (Zatorre, 2013). This genetic-environment cross-talk could explain why some genetic factors might underlie the motivation of some individuals to start these special trainings, stressing the important role of genetic predispositions in actively selecting specific niches that reinforce the development of certain skills based on those predispositions (see Scarr & McCartney, 1983). As a possible alternative, investigating musical learning in non-musicians may contribute to disentangle the contribution of the different processes underlying musical skills. Indeed, the potential differences in brain structure and function across non-musician individuals can hardly be explained by the effect of intensive (musical) practice. In this sense, the present study aimed to investigate the extent to which WM microstructural organization predicts individual abilities to learn music in non-musicians. Based on previous music learning paradigms, we designed a behavioural protocol in which Fast Music Learning (FML) was assessed. Participants were trained in a rhythm-synchronization and a piano melody learning tasks in a single session fixed protocol, without further opportunities for consolidating the learning.

Rhythm synchronization abilities have been mainly studied by comparing musicians and non-musicians (Patel, 2005; Bailey & Penhune, 2010, 2012; Chen et al., 2008a, 2008b). At the behavioural level, rhythm synchronization abilities have been related to auditory working memory and formal musical training (Bailey & Penhune, 2010). At the neural level, Chen and collaborators (2008a) have used fMRI to show in non-musicians that an increasing inter-tap-interval deviation (a measure of how similar is the subjects' pattern response compared to the metrical structure of the model stimuli) during a rhythmic-synchronization task correlates with changes in activity in premotor regions (supplementary motor areas –SMA and pre-SMA–, as well as dorsal and ventral premotor cortices –dPMC, vPMC–), dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), inferior parietal lobule (IPL), thalamus, and cerebellum lobule VI. Furthermore, functional connectivity analysis revealed that activity in bilateral auditory cortices correlated with the activity in the right dPMC (Chen et al., 2008a), highlighting the role of audio-to-(pre)motor interactions in rhythm learning (see also Ripollés et al., 2015; Rodríguez-Fornells et al., 2012). Interestingly, an fMRI study with non-musicians has revealed that similar motor regions are involved in the passive perception of rhythmic sequences, when no movement was allowed (Bengtsson et al., 2009). Moreover, activity in the prefrontal cortex was modulated by complexity of the perceived rhythmic sequences (Bengtsson et al., 2009). Using PET data, Ramnani & Passingham (2001) described a complex pattern of increases and decreases in activation in the mentioned areas in relation to learning a rhythmic sequence paced by visual cues. These authors proposed different stages in the acquisition of temporal sequences: (i) early attention to the stimuli might be related to prefrontal cortex activation; (ii) translation of the learned sensory rhythm into motor representations might involve parietal regions; (iii) preparation of the paced movements learned might activate premotor regions (PMC/pre-SMA); and (iv) storage of the motoric representation of the rhythms into motor memory might involve the coordinated activity of the cortico-cerebellar loops (Ramnani & Passingham, 2001).

On the other side, learning to play a melody and the construction of auditory-motor associations in a specific musical context has been less explored. Lahav and colleagues (2007, 2013) have observed that non-musician subjects are able to learn how to play a musical piece in the piano, even after only one session of practice (Lahav et al., 2013). Moreover, these authors found that participants that recently learned how to play a melody in the piano, when presented with that melody after the training, activated a frontoparietal motor-related network (including Broca's area, premotor regions, intraparietal sulcus, and the inferior parietal area) during pure listening, without performing any movements (Lahav et al., 2007). These authors interpret their findings in a mirror-neuron-related framework, hypothesizing that this frontoparietal network may be part of an action recognition system that is selectively activated and dependent on the individual's motor repertoire. Hence, they conclude that acquiring actions closely linked with an auditory output seems to quickly generate a functional link between the sound of those actions and the corresponding motoric representations (Lahav et al., 2007). Furthermore, Chen and collaborators (2012) studied the neural regions activated during learning to play melodies on a piano keyboard, and showed that melody learning was mainly related to changes in neural activity in the vPMC bilaterally and in the left dPMC. These authors also observed that better performance was significantly correlated with less neural activity in the left dPMC (Chen et al., 2012). In a more recent study, Herholz and collaborators (2015) scanned non-musician subjects before and after a 6-weeks piano training. These authors found that more activity in the right auditory cortex and right hippocampus, and less activity in the superior and medial orbitofrontal cortices and bilateral subcallosal (rectus) cortices during a pre-training listening fMRI task predicted higher learning rates. This study highlights the important role of pre-learning brain functional connectivity as predictors of future learning success. Regarding brain structural correlates of melody learning, Engel and colleagues (2014) found that non-musician individuals with faster melody-learning rates had higher fractional anisotropy (FA) values in the corticospinal tract bilaterally and in the right superior longitudinal fasiculus. The superior longitudinal fasciculus (SLF) is a WM bundle connecting parietal and frontal areas, and it is divided in three different segments (SLF I, II and III). The arcuate fasciculus (AF) is a WM structure connecting IFG, parts of premotor, insular cortex and medial frontal regions, with inferior parietal regions (i.e., supramarginal and angular gyri), and with the superior temporal gyrus. The AF is also divided in three segments: the direct or long segment communicating the IFG with the superior temporal cortex; the posterior segment connecting superior temporal with inferior parietal areas; and the anterior segment which connects inferior parietal regions with inferior and medial frontal areas. Alternative classifications describe the AF with only two segments (long and posterior), assuming the anterior segment of the AF might correspond with the SLF-III (Fernández-Miranda et al., 2015; Wang et al., 2016; Bozkurt et al., 2016).

In addition to these learning paradigms, patient studies have also contributed to our knowledge regarding the neural substrates of melodic and rhythmic processing. Pitch deafness, the most common type of congenital amusia (affecting pitch discrimination, dissonance perception, melody discrimination and melody recognition, among other musical skills), is associated with poor connectivity between the auditory cortex and the inferior frontal gyrus, mainly on the right hemisphere (Peretz, 2001; Hyde et al., 2011). However, Phillips-Silver and colleagues (2013) observed that when the pitch dimension is eliminated from the stimuli to imitate or synchronize to (substituting pitched piano tones for non-pitched drum timbres), amusics show normal metre recognition, as well as intact ability to synchronize their movements to the beat. This is in line with previous research, showing different neural origins in pitch deafness compared to beat deafness (Hyde et al., 2011; Phillips-Silver et al., 2013). As a matter of fact, Di Pietro and colleagues (2004) observed a clear dissociation between melodic and rhythmic discrimination processes in a single case of acquired amusia in a former professional musician. In this report, the patient suffered an infarct involving the superior and middle temporal gyri, as well as the inferior parietal lobe, and showed a particular impairment in writing down the rhythmic component of heard music, as well as in discriminating and reproducing rhythmic sequences by ear. Interestingly, the ability to perform these same tasks by visual presentation of the rhythmic patterns or by using melodic stimuli was intact (Di Pietro et al., 2004). Finally, a recent study in stroke patients have reported that poor rhythm discrimination abilities were associated with lesions in the right basal ganglia, while poor pitch/scale discrimination aptitude was associated with lesions in right superior temporal regions (Sihvonen et al., 2016).

However, there is a clear lack of studies investigating the link between individual differences in WM structural connectivity and music learning abilities in healthy subjects with no musical background. Considering previous fMRI and structural correlates of music processing, we selected several WM pathways that could be important in predicting music learning skills. An interesting study focused on WM microstructural properties related to musical practice (Bengtsson et al., 2005) found that the only region differing in FA between musicians and non-musicians was the posterior limb of the internal capsule (PLIC), a subcortical structure crossed by the corticospinal tract in its trajectory to the sensorimotor cortices. Moreover, these authors found that musical practice during adulthood was correlated with a fibre bundle in the right temporo-parietal junction, which was assumed to pertain to the AF (Bengtsson et al., 2005). Surprisingly, Bengtsson and colleagues (2005) did not discussed much about these results found for the right AF, despite the interesting debate that the role of this WM structure in music learning could motivate. Hence, based on these previous results, we decided to restrict our analyses to the corticospinal tract (Bengtsson et al., 2005; Engel et al., 2014) and the AF (Bengtsson et al., 2005; Engel et al., 2014; Halwani et al., 2011; Loui et al., 2011; Oechslin et al., 2010), which have connections to sensorimotor, auditory and multisensory integration cortical regions of the brain.

Considering these pathways, we hypothesized that the corticospinal tract may predict the performance in the rhythm learning task (due to its crucial role in fine-motor control) (Bengtsson et al., 2009; Chen et al., 2008 a, b; Engel et al., 2014). For melodic learning and considering the importance of recruiting audio-(pre)motor networks during this task (Chen et al., 2012; Rodríguez-Fornells et al., 2012), we predicted larger involvement of the AF. A slight lateralization bias to the right AF was predicted considering the role of the right auditory cortex in pitch discrimination and perception (Albouy et al., 2013; Coffey et al., 2016; Herholz et al., 2015; Hyde et al., 2006, 2007; Johnsrude et al., 2002; Zatorre et al., 2002, 2007), tonal or melodic pattern processing (Foster & Zatorre, 2010; Johnsrude et al., 2000; Patterson et al., 2002; Peretz et al., 1990), tonal working memory (Albouy et al., 2013; Grimault et al., 2014), as well as in processing speech contours and prosody (Loui et al., 2011; Sammler et al., 2015). In addition, involvement of the right AF was expected also due to the crucial involvement of the right IFG in melodic processing (Albouy et al., 2013; Bermudez et al., 2009; Chen et al., 2012; Herholz et al., 2015; Hyde et al., 2006, 2007), as well as the important role of these same areas (i.e., IFG and auditory cortex) in the left hemisphere for performing auditory-motor transformations (López-Barroso et al., 2013; Vaquero et al., 2016).

5.2 Methods

5.2.1 Participants and testing sessions

44 healthy native Spanish-Catalan speakers (mean age: 22.16 ± 2.56; 28 females) participated in this experiment. All but 10 were proper non-musicians, with no music training aside from the mandatory lessons in primary and secondary school. The other 10 had assisted to some music lessons, either for no more than 3 years and at least 10 years ago, or for less than one consecutive year but less than 10 years ago (this included 2 months to 3 years of music theory lessons, choir rehearsals, guitar, piano, saxophone, or Jew's harp lessons). In order to control for this musical experience, we calculated the amount of hours of music lessons until the moment of the test (received both in school and in music-schools, if applicable). To do so, we took into account the information recorded by the subjects in an initial questionnaire, in which they had to answer the hours of music lessons per week they had during primary school, high school and, if applicable, the amount of time they have assisted to music lessons aside from the mandatory education. Mean hours of music lessons for the whole sample was 696.6 ± 254.9; for the proper non-musicians (n = 34) was 676.1 ± 246.2; for subjects with some musical training (n= 10) was 766.4 ± 285. None of the participants reported any neurological, psychiatric or auditory disorder.

Participants underwent (i) an MRI session in which T1-weigthed and DTI data was obtained, and (ii) in a different session (always after the MRI session), participants performed a behavioural testing protocol in which they had to complete a rhythm-synchronization task and a melody learning task. In the behavioural session the order of the tasks was: 1) before coming to the lab, participants filled an initial questionnaire; 2) the day of the session, all participants started with the rhythm synchronization and the melody learning tasks (counterbalanced across subjects); 3) then, for screening purposes, they completed tasks 3 and 4 from the Montreal Battery of Evaluation of Amusia (MBEA, Peretz et al., 2003), which allowed us to discard any potential amusic participant (all participants scored above chance level and no subject was discard based on their MBEA performance). All subjects were naïve to the hypothesis of the study, gave their written informed consent to participate, and received monetary compensation for their participation.

5.2.2 Music learning tasks

For all the musical tasks, the auditory stimuli were delivered through *Senheiser* stereo headphones at a comfortable intensity level, adjusted for each participant. Participants responses were recorded through different response devices (a MIDI-keyboard or a mouse, depending on the task), with tasks implemented in EventIDE (for melody learning tasks; Okazolab Ltd, 2012) and Presentation (for rhythm synchronization task; Neurobehavioral Systems) software on a PC computer.

5.2.2.1 Rhythm synchronization task

This is an adaptation of tasks used in previous rhythm learning studies (Bailey & Penhune, 2010; Chen et al., 2008 a, b; Padrão et al., 2014). In this task subjects were challenged to reproduce 5 different auditory rhythmic sequences (2 easily-learning rhythms, followed by 3 more-complex rhythms, always following the same order).

Each rhythm consists of 11 woodblock notes with the same pitch, with a total duration of 6 seconds. Rhythms differ in their temporal structure, so the interval following each sound varied such that five different musical durations (onset-to-onset) were created. Each rhythm contained: five-eight notes (each 250 ms), three quarter notes (each 500 ms), one dotted quarter note (750 ms), one half note (1000 ms) and one dotted half note (1500 ms).

The task was divided in 5 fixed blocks (from easier to more complex rhythms). In each block subjects were tested with only one of the rhythms along 12 trials, allowing the assessment of learning. Each trial included two steps always following the same order: (i) *Listening*, subjects listened carefully to the rhythm avoiding any type of motor imagery exercise or movement related to rhythm reproduction (e.g., foot-tapping, nodding to the beat), and (ii) *Synchrony*, consisting on tapping (with their right index finger in the left button of the PC-mouse) as accurately as possible, synchronizing their motor responses with each tone of the rhythmic model.

The beginning of each condition was signalled with a warning tone presented 500 ms before the target sequence. Participants had to perform the rhythmic sequences without stopping to correct errors and they had to try to follow the rhythm even when not being sure about the structure. At the beginning of the task, participants practiced with two different rhythms (not included later in the learning protocol) for two trials, in order to familiarize them with the stimuli and what they were expected to do. There was no feedback administered after this initial training block, but the number of the current trial and rhythm was displayed in the screen with every change of trial and rhythm respectively.

When correcting this task, we observed that rhythm 4 was extremely difficult and no single participant was able to learn it. Consequently, we decided to remove this rhythm and focus our analyses on the average of the remaining four rhythms (i.e., 1, 2, 3, and 5).

Performance and learning were evaluated through three different variables: (i) the absolute value of mean asynchrony (mASY), to investigate how accurate was the synchronization of the subject to the listened model; (ii) the percentage correct (PC) responses, calculated as the percentage of responses (taps) made within half of the onset-to-onset interval before and after a woodblock note (model tap or inter-stimulus interval); (iii) the Inter-Tap-Interval deviation (ITI-deviation), a measure of how well adapted is the participant's response pattern compared to the model sequence; it is calculated as a ratio of the ITI and the inter-stimulus interval (ISI) subtracted from 1 (Bailey & Penhune, 2012). A scheme of the musical tasks and the extraction of the performance variables is displayed in Figure 5.1 (C, D, for the rhythm synchronization task).

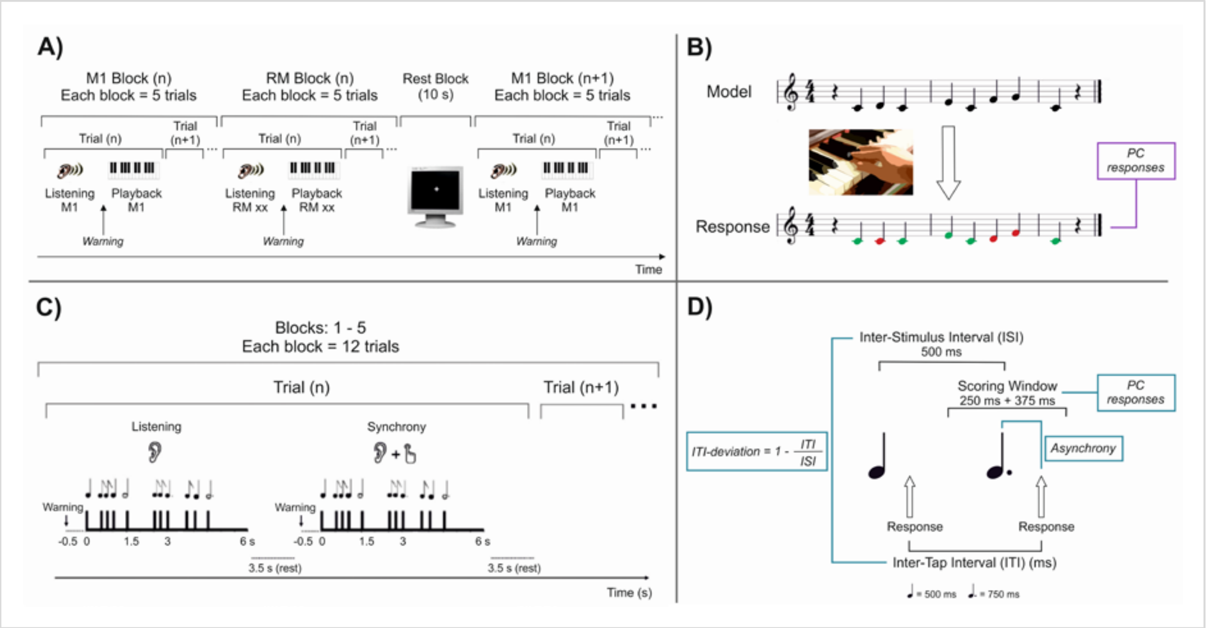

Figure 5.1. Schematic representation of the musical tasks and their measures of learning (top row corresponds to the melody task, bottom row pertains to rhythm). A) Melody learning task's scheme: blocks of the trained melody (M1) and random melodies (RM: control condition) were intercalated, with resting breaks of 10 seconds after each pair of M1 and RM blocks; this scheme was repeated until reaching block number 8, both for the M1 and the RM. B) Responses in the melody learning task and measure extracted. C) Scheme of the rhythm task: each block contained only one of the rhythms, and there were 12 consecutive trials per block. D) Responses for the rhythm task and learning-parameters extracted. Abbreviations: M1, trained melody; RM; random melody;

PC, percentage correct responses; ITI-deviation, inter-tap-interval deviation.

5.2.2.2 *Melody learning task*

This task is inspired on the one recently used in an fMRI study by Chen and colleagues (2012). A Yamaha PSR-E343 MIDI keyboard was used as the response device. Since the aim of the task was to study purely audio-motor associations, in order to avoid the visual feedback and interference given by the sight of the keyboard in which subjects had to deliver their responses, a box with a little window with enough space for positioning the hand and allowing the movement along the 8 keys needed for the task, was placed covering the keyboard (similar as the mechanism used by Engel and collaborators, 2014).

The task was divided in five steps: (1) *Familiarization with the keyboard*: subjects had to listen and exercise five 8 pitch-sequences across 10 trials (2 repetitions of each sequence), with a 2-step structure: (i) listening to the sequence, (ii) synchronization, in other words, playback the sequence at the same time they listened to it again. The 5 sequences increased their difficulty progressively: first sequence reinforced each pitch individually (C4-C4-C4-C4-D-D-D-D-E-E-E-E-F-F-F-F-G-G-G-G-A-A-A-A-B-B-B-B-C5-C5-C5-C5), the second one increased the pitch sequentially and then went back down (C4-D-E-F-G-A-B-C5-B-A-G-F-E-D-C4), the third one alternated the pitches in an increasing way (C-E-D-F-E-G-F-A-G-B-A-C5), the fourth sequence alternated the tones in a decreasing way (C5-A-B-G-A-F-G-E-F-D-E-C4), and the fifth one tried to give the participants the idea of how an increasing and a decreasing movement across the keys may sound (C4-D-E-D-C4-D-E-F-E-D-E-F-G-F-E-F-G-A-G-F-G-A-B-A-G-A-B-C5-B-A). (2) *Perception phase*: participants had to listen to 2 melodies, Melody 1 (M1: C4-D-C4-E-C4-F-G-C4) and Melody 2 (M2: D-G-F-G-D-E-F-C4) without knowing they will had to learn to play the M1 later on. Each melody contained 5 quarter notes and, after the editing process, both of them had a total duration between 500 and 600 ms. There were five blocks, each one consisting in: M1 and M2 presented for two consecutive trials (M1-M1-M2-M2, or M2-M2-M1-M1, counterbalanced across participants) and four trials of silence. (3) *Training phase*, containing 8 blocks with 5 repetitions of each of the conditions in each block: (i) *Melody Listen & Melody Playback*: first, subjects had to listen to M1 and, after that, they had to play it by memory; (ii) *Random melody Listen & Random melody Playback* (random melodies contained the same pitches as the M1, but the order of them for every paired listen-playback trial was unique and different), which is an interesting condition that could reinforce the auditory association with each pitch, but not the learning of the M1 contour; (iii) *Rest* in silence for 10 seconds. These three steps were fixed and the only aspect that changed was the Random melody Listen & playback condition, since the order of the random melodies (RM) presented in those blocks were randomized across participants.

Performance was measured by calculating the percentage of correct notes (those that match the expected pitch) performed per trial, both for the trained melody (M1) and for the random melodies. Due to problems with the software used in this task, we finally could include only the behavioural data from 31 participants. See Figure 5.1 (A, B) for a schematic representation of the melody task and its correction.

5.2.3 Imaging acquisition and analyses

Diffusion Tensor Imaging (DTI: spin echo diffusivity sequence) data was obtained from a 3.0 T Discovery mr750w General Electric scanner (Barcelona, Spain). Due to several technical problems with the scanner and movement artifacts present in some subjects' data, only 36 DTI images could finally be included in the imaging analyses.

Imaging parameters for the DTI sequence were: TR = 12825.00 ms, TE = 9ms; FOV = 128 x 128 x 57 mm; matrix size = 128 x 57; slice thickness = 2.0 mm; no gap; 57 axial slices; voxel size was 2 x 2 x 2 mm. Diffusion was measured along 72 non-collinear directions, using a b value of 1000 s/mm2, and including a b=0 as the first volume of the acquisition as well as 8 additional b=0 intercalated each 8 volumes.

5.2.3.1 DTI - preprocessing and manual dissection

To pre-process the diffusion-weighted images, first, the brain was virtually separated from the rest of the head using FSL's Brain Extractor Tool (Smith, 2002; Smith et al., 2004; Woolrich et al., 2009). Afterwards, motion and eddy-current correction was performed using FMRIB's Diffusion Toolbox (FDT), part of the FMRIB Software Library (FSL 5.0.1 www.fmrib.ox.ac.uk/fsl/). The b-vectors gradient matrix was then rotated in order to take into account the corrections made at the previous stage, by using the *fdt_rotate_bvecs* software included in the FMRIB Software Library. The diffusion tensors were then reconstructed using Diffusion Toolkit's least-square estimation algorithm for each voxel, and Fractional Anisotropy (FA) was calculated (Ruopeng Wang, Van J. Wedeen, Martinos Center for Biomedical Imaging, Massachusetts General Hospital, http://www.trackvis.org/).

Whole-brain deterministic tractography was performed in Diffusion Toolkit, using an interpolated streamlines algorithm, with a maximum curvature threshold of 35 degrees and a minimum FA threshold of 0.2. The fibre direction is assumed to correspond to the principal eigenvector (the eigenvector with the largest eigenvalue). This vector was colour coded (green for anterior–posterior, blue for superior–inferior and red for left–right directions) in order to generate a colour–coded FA map. Dissections were carried out for each subject in the native space and in both hemispheres, using Trackvis software. The regions of interest (ROIs) were defined on the FA and FA colour-coded maps according to individual anatomical landmarks, instead of atlas-based constraints which neglect individual differences (López-Barroso et al., 2013). As previously explained, based on previous literature (mainly Bengtsson et al., 2005; Engel et al., 2014) we decided to dissect the Arcuate Fasciculus and the Corticospinal tract.

Arcuate Fasciculus (AF)

The three segments of the AF were dissected using three main manually defined ROIs as described in previous studies (Catani et al., 2005, 2007; López-Barroso et al., 2013). Specifically, a first ROI was delineated in the coronal view, anterior to the central sulcus, encompassing the fibres going to the inferior frontal gyrus (including Broca's area; Brodmann's areas 44 and 45, and parts of the medial frontal gyrus). Then, in the axial slice a second ROI was depicted covering the WM underlying the medial and superior temporal gyrus (embracing the fibers traveling to Wernicke's territory; Brodmann's areas 22p, 41 and 42). Finally, a third ROI was drawn on the sagittal view, covering supramarginal and angular gyri and encompassing the fibers traveling to Geschwind's territory (Brodmann's areas 39 and 40). These ROIs were combined to encompass the three rami of the AF: the long (between IFG-Broca's and STG-Wernicke's areas), the anterior (linking IFG-Broca's and Geschwind's territories) and the posterior (connecting Wernicke's and Geschwind's territories) segments. Artefactual fibers were removed using exclusion ROIs.

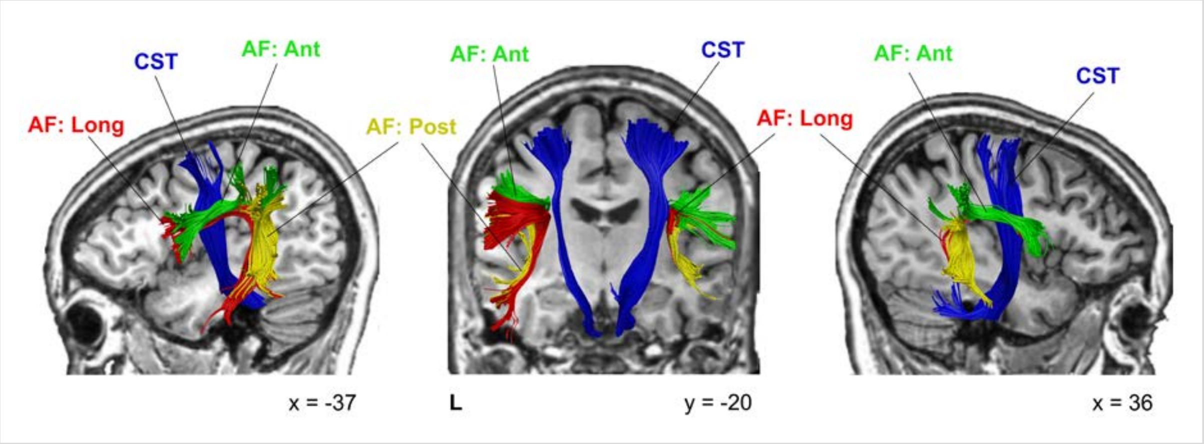

Figure 5.2. Depiction of the bilateral dissection of CST and AF in an example subject. Colour code: blue, CST; red, long segment of the AF; green, anterior segment of the AF; yellow, posterior segment of the AF. Abbreviations: CST: corticospinal tract; AF: arcuate fasciculus; Ant: anterior segment; Post: posterior segment.

Corticospinal tract (CST)

The CST was isolated using three main ROIs. Specifically, to track CST fibers, first the cerebral peduncle and the posterior limb of the internal capsule ROIs were delineated on the colour-coded FA map, in the axial view. Then, the WM underlying the precentral and postcentral cortex (Brodmann's areas1, 2, 3 and 4) was then selected also in the axial view, on the regular FA map, which allows a better anatomical localization than the FA-colour map. Any artefactual fibres were removed using exclusion ROIs. See Figure 5.2 for an example of the fibre-tract dissection in one subject.

As we have previously done (Vaquero et al., 2016), we restricted our statistical analysis to FA and volume measures since recent investigations have shown that these WM parameters are very sensitive to individual differences (Saygin et al., 2013; Ocklenburg et al., 2014; Sreedharan et al., 2015). We extracted the volume and the FA from the bilateral CST and the bilateral whole AF (summing up the values from each of the three AF segments, as previously performed, Vaquero et al., 2016). In a secondary analysis, we checked the results for the three rami of the AF separately. Pearson correlations between the WM related measurements and the music learning values, both for rhythm synchronization and melody-learning tasks, were performed, always controlling for the amount of hours of music lessons. Significance of all the reported results was thresholded at a $p < 0.05$. *P*-values where adjusted for non-sphericity using the Greenhouse-Geisser test when appropriate.

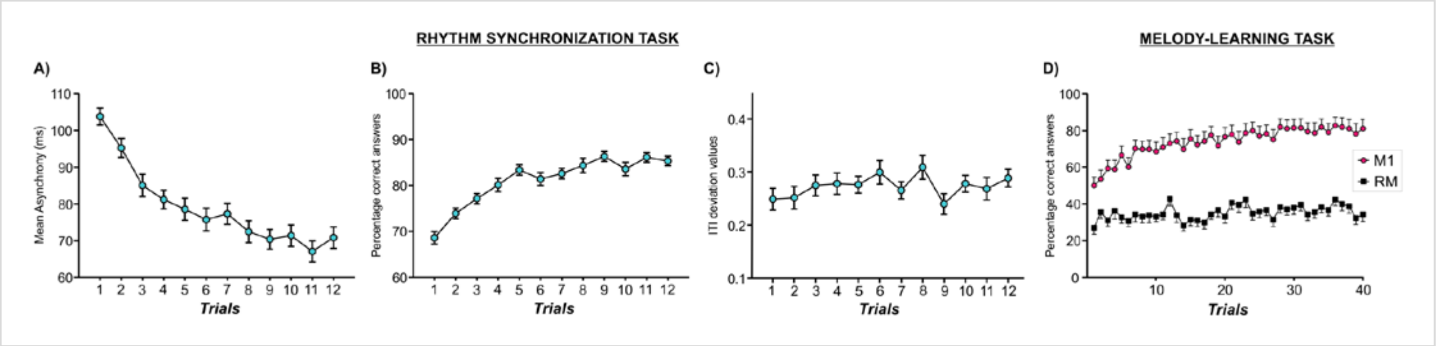

Figure 5.3. Learning curves depicting the mean performance across subjects in each trial. First three graphs correspond to the *rhythm synchronization task*. A) Mean absolute values of asynchrony: asynchrony is reduced throughout the task. B) Percentage correct (PC) responses in the rhythm task: PC increases trial by trial. C) Inter-tap-interval deviation (ITI-deviation): there is not a clear pattern of reduction or increase of this variable along the task. The last graph on the right (D) corresponds to the *melody learning task*: pink circles show the learning curve for melody 1 (the only melody that was repeated throughout the task), black squares show the performance for the random melodies (RM); performance for the M1 increased trial by trial, while there was no indicator of improvement for the RM.

5.3 Results

5.3.1 Behavioural results: learning of musical tasks

5.3.1.1 Rhythm task

As shown in Figure 5.3 (panels A, B, C), and despite the great individual variability in the performance exhibited by the participants in this task, the mean of the group evidenced a clear improvement in mean asynchrony throughout the 12 trials (paired t-test between first and last trials: mean mASY 1st trial = 103.8, SEM = 2.3, mean mASY trial 12th = 70.9, SEM = 2.9; $t(43) = 10.1$, $p < 0.0001$) and percentage correct (paired t-test between first and last trials: mean PC 1st trial = 68.6, SEM = 1.4, mean PC trial 12th = 85.3, SEM = 1.02; $t(43) = -9.4$, $p < 0.0001$): mASY was reduced while percentage correct responses increased trial by trial (see Table 1 for correlation values of rhythm measures). However, there were no significant differences in the ITI-deviation values along the task (paired t-tests comparing all trials with the first one were non-significant; detail for the comparison between the first and last trials: ITI-deviation 1st trial = 0.3, SEM = 0.02, ITI-deviation 12th trial = 0.29, SEM = 0.02, $t(43) = -1.3$, $p = 0.193$), and thus for the rest of the analyses we decided to calculate a grand average of ITI-deviation that accounted for the difference between the rhythmic pattern performed by the participants and the external model, across the whole task.

5.3.1.2 Melody task

As depicted in Figure 5.3 (panel D), participants improved in their percentage correct (melody PC) responses throughout the 40 trials, despite the individual variability displayed by the participants regarding the performance in this task (see individual data points for improvement in performance in Figure 5.4). This improvement, however, was specific for the trained melody (M1). Conversely, no improvement was observed in the random-melodies performance: no significant change across trials either when comparing last and first trials (paired t-test between first and last trials for M1: mean PC 1st trial = 50, SEM = 5.3, mean PC trial 40th = 81.1, SEM = 5.7; $t(30) = -5.1$, $p < 0.0001$; paired t-test between first and last trials for RM: mean PC 1st trial = 27, SEM = 4.02, mean PC trial 40th = 34.3, SEM = 4.4; $t(30) = -1.5$, $p = 0.15$), or when comparing the global performance in RM and M1 (repeated-measures ANOVA showed a significant interaction of melody type –M1, RM– and trial number, $F(1,39) = 2.3$, $p < 0.01$). Moreover, paired t-test between M1 and RM in each trial showed significant differences across the 40 trials, with increasing differences in parallel with the progression of the task (t-test for the first trial: mean M1 1st trial = 50, SEM = 5.3, mean RM 1st trial = 27.02, SEM = 4.02; $t(30) = 3.7$, $p < 0.001$; t-test for the last trial: M1 40th trial = 81.1, SEM = 5.7, mean RM 40th trial = 34.3, SEM = 4.4, $t(30) = 8.2$, $p < 0.0001$).

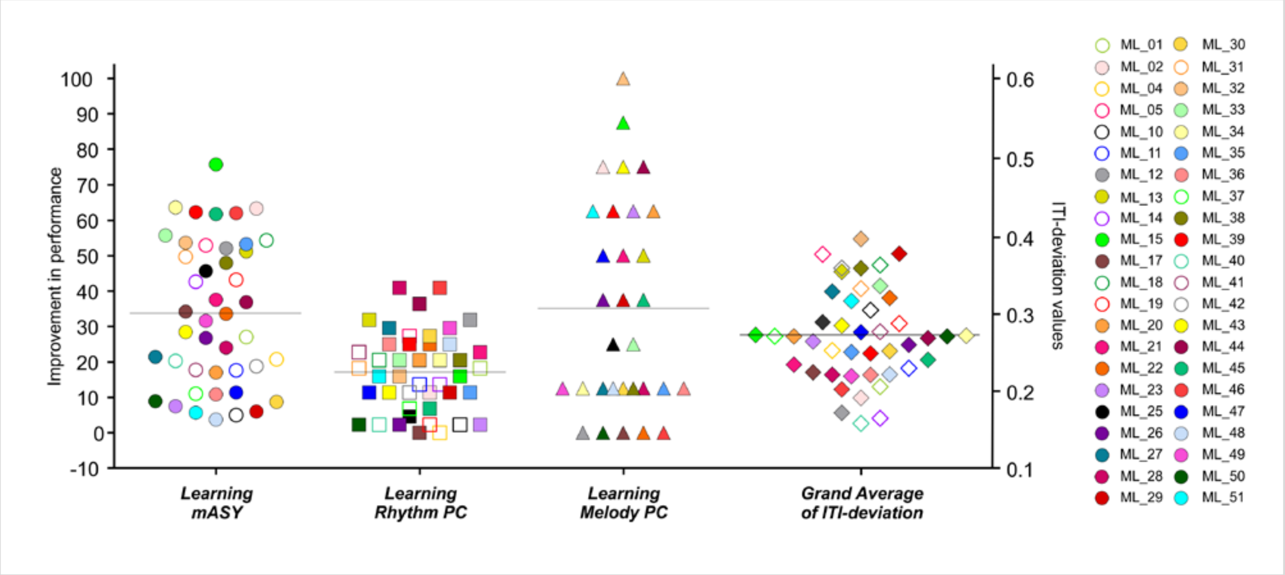

Figure 5.4. This graph depicts the distribution of our cohort in learning or performance in the different aspects of the FML paradigm. From left to right: circles correspond to learning in mASY (mean absolute values of asynchrony); squares show distribution for improvement in percentage correct (PC) responses in the rhythm task; triangles correspond to improvement in percentage correct responses in the melody task; diamonds depict the distribution of the grand average of ITI-deviation (inter-tap-interval deviation). Open figures (circles/squares/diamonds) correspond to those participants who completed the rhythm task but not the melody task, filled figures show the participants who completed both the rhythm and the melody task; each subject is coded with a different colour. Horizontal lines depict the group mean for each measure.

5.3.2 Behavioural relationship between musical tasks

Both for the Melody Learning and for the Rhythm synchronization tasks, we were interested in studying the behavioural improvement between initial performance and the level of achievement at the last trial. Motivated by this, instead of calculating an averaged performance measure across all trials and sessions of practice (as it has been reported in previous motor learning paradigms, Savion-Lemieux et al., 2009; Watanabe et al., 2007), we decided to perform paired t-tests between initial and final performance (Karni et al., 1998) for each of the musical measurements, in order to assure the improvement in performance. Since significant differences between baseline and final performance were found for all measurements, we calculated a learning rate following the formula: (final performance – initial performance) / initial performance, which reflects the particular amount of change for each participant taking into account the baseline performance (see for a discussion Dimitrov & Rumrill, 2003). The only exception was ITI-deviation, for which we did not find significant improvement and thus, we performed a Grand Average, using a measure of performance similar to the one used in previous motor-learning reports (Savion-Lemieux et al., 2009; Watanabe et al., 2007). See Figure 5.4 for a depiction of the distribution of learning in different music-tasks variables and the distribution of the average of ITI-deviation.

Besides, for measuring the speed of the behavioural change associated to learning in the musical tasks, we computed the minimum number of trials needed by the subjects to reach 70% of correct responses, both in the melody learning and the rhythm synchronization tasks. In the case that the subject never reached 70% correct responses, we assigned a score corresponding to the maximum number of trials contained in the task, 12 for rhythm synchronization, and 40 for melody learning.

Notice that this measure reflects learning speed and is less affected than change-related measures (as the above defined *learning rate*) by initial individual differences in performance (1st trial in this case) (Engel et al., 2014; Golestani et al., 2002, 2004). Change-related measures (derived from computing the subtraction between final vs. initial performance scores) are very affected by the existing range of improvement available for each individual. For example, a participant with very good score in motor learning at the initial data point, might have a small improvement rate value because the initial point of departure was already high. In this sense, learning speed and learning rate tend to correlate negatively (as lower learning rates are associated to better performance or faster speed) (see Table 1).

	Rhythm PC 1st trial	mASY 1st trial	Learning rate for Rhythm PC	Learning rate for mASY	Grand Average of ITI-deviation	Learning Speed for Rhythm	Melody PC 1st trial	Learning rate in Melody PC	Learning Speed in Melody
Rhythm PC 1st trial			***r* = -.87** ***p* = .00**			***r* = -.83** ***p* = .00**			
mASY 1st trial				r = .28 *p* = .07				r = .29 *p* = .13	
Learning rate for Rhythm PC	***r* = -.87** ***p* = .00**					***r* = .8** ***p* = .00**			
Learning rate for mASY		r = .28 *p* = .07							***r* = -.39** ***p* = .03**
Grand Average of ITI-deviation									
Learning Speed for Rhythm	***r* = -.83** ***p* = .00**		***r* = .8** ***p* = .00**						
Melody PC 1st trial								***r* = -.6** ***p* = .00**	***r* = -.49** ***p* = .01**
Learning rate in melody PC		r = .29 *p* = .13					***r* = -.6** ***p* = .00**		
Learning speed in Melody				***r* = -.39** ***p* = .03**			***r* = -.49** ***p* = .01**		

Table 5.1. Correlations across all the variables of learning for both music tasks (rhythm and melody). Bold letters show the significant correlations. Comparisons among the rhythm task parameters (white cells) have a sample size: n = 44; comparisons among the melody task parameters or for the rhythm compared to the melody task (violet-shaded cells) have a sample size: n = 31. All values are rounded to a maximum of two decimals, and only those correlations with $r \geq 0.25$ are shown. Abbreviations: PC, percentage correct; mASY, absolute values of mean asynchrony; ITI-dev, inter-tap-interval deviation.

Initial performance (at 1st trial), learning rate, the grand average of ITI-deviation, and the index of learning speed, were included in the Pearson correlations carried out with the imaging data, always controlling by the amount of hours of music lessons.

Table 5.1 summarizes the correlations between different variables of the musical tasks (rhythm and melody learning measurements compared between them). At an intra-task level, all the percentage correct-related measures were correlated, both in the rhythm task (PC at 1st trial with Learning rate of PC: r = -0.87, $p < 0.0001$; PC at 1st trial with Learning speed in rhythm: $r = -0.83$, $p < 0.0001$) and in the melody task (PC at 1st trial with Learning rate of PC: $r = -0.6$, $p < 0.001$; PC at 1st trial with Learning speed in melody: $r = -0.49$, $p < 0.01$). For example, across learning tasks, we found that values of learning rate in mASY predicted the learning speed in the melody task ($r = -0.47$, $p < 0.05$): the greater the learning rate of mASY (the bigger the difference between initial and last trials), the smaller the number of trials needed to reach 70% of correct responses in the melody learning task.

5.3.3 Tractography correlations

For the correlations between the dissected tracts and musical tasks performance, it is important to notice that different sample sizes are used due to the problems experienced in the melody learning task and encountered in the DTI data: for rhythm comparisons, $n = 35$; for melody correlations, $n = 24$.

5.3.3.1 Primary analysis

Corticospinal tract

Only one of the behavioural variables was significantly correlated with the DTI measures from the bilateral CST: rhythm task's PC in the 1st trial was positively correlated with volume of the right CST ($r = 0.36$, $p < 0.05$). This means that the greater the volume in the right CST, the better the initial performance in the rhythm task (the higher the PC). See Figure 5.5 for the corresponding scatterplots and Table 5.2 for the details of these correlations.

Whole Arcuate Fasciculus

Several music-learning measurements significantly correlated with the AF. Specifically, volume on the right AF was positively correlated with learning rate of mASY ($r = 0.36$, $p < 0.05$); in other words, the greater the volume of the right AF, the higher the learning rate (the greater the difference between first and last trials). Moreover, the minimum amount of trials needed for reaching 70% correct responses in the melody task was negatively correlated both with volume ($r = -0.58$, $p < 0.005$) and FA ($r = -0.52$, $p < 0.05$) of the right AF, which means that the greater the volume and the better the microstructural organization of the right AF, the faster the learning of melodies in the piano (the smaller the number of trials needed to reach 70% of correct responses). See Figure 5.5, which depicts the scatterplots for these primary correlational results, and Table 2, which contain more details about these correlations.

	Rhythm PC 1st trial (n=35)	*mASY 1st trial (n=35)*	*Learning rate rhythmPC (n=35)*	*Learning rate mASY (n=35)*	*Grand Average ITI-dev. (n=35)*	*Learning speed Rhythm (n=35)*	*Melody PC 1st trial (n=24)*	*Learning rate Melody (n=24)*	*Learning speed Melody (n=24)*
L CST volume				r = -.28 *p* = .11	r = -.26 *p* = .13			r = -.33 *p* = .13	r = .3 *p* = .16
L CST FA					r = -.34 *p* = .05				
R CST volume	***r =.36*** ***p = .04***		r = -.32 *p* = .07			r = -.29 *p* = .09	r = .29 *p* = .18	r = -.3 *p* = .17	
R CST FA					r = -.3 *p* = .08				
L AF volume									
L AF FA									
R AF volume	r = .26 *p* = .14			***r = .36*** ***p = .04***					***r = -.58*** ***p = .00***
R AF FA		r = -.31 *p* = .07							***r = -.52*** ***p = .01***
L Long volume							r = .38 *p* = .07	r = -.3 *p* = .18	
L Long FA	r = -.29 *p* = .1		r = .29 *p* = .1		r = -.25 *p* = .16				
L Ant volume									r = .31 *p* = .15
L Ant FA									
L Post volume							r = -.29 *p* = .18	r = .34 *p* = .12	
L Post FA								r = .33 *p* = .14	
R Long volume									r = -.38 *p* = .08
R Long FA		r = -.29 *p* = .1							***r = -.42*** ***p =.05***
R Ant volume				***r = .55*** ***p = .00***				r = .41 *p* = .06	
R Ant FA	r = -.33 *p* = .06								
R Post volume	r = .27 *p* = .12		r = -.25 *p* = .15						
R Post FA					***r = -.35*** ***p = .04***				r = -.27 *p* = .21

Table 5.2. Details of the correlations between the DTI measures and the performance measurements from both the melody and the rhythm tasks (sample size is given in brackets for each music-learning measure). Shaded cells and bold italic letters show those significant results at $p < 0.05$, after controlling by the amount of hours of music lessons. All values are rounded to a maximum of two decimals, and only those correlations with $r \geq 0.25$ are shown. Abbreviations: PC, percentage correct; mASY, absolute values of mean asynchrony; ITI-dev, inter-tap-interval deviation; L, left; R, right; CST, corticospinal tract; AF, arcuate fasciculus; Ant, anterior segment of the AF; Post, posterior segment of the AF; FA, fractional anisotropy.

As seen in Figure 5.5 (C, D), the variable accounting for learning speed in the melody task, has a very polarized distribution that could be affecting the estimated correlation value. Hence, for explorative purposes, we decided to seek for differences between fast and slow learners of piano melodies. We divided our sample in two groups: fast melodic learners (minimum amount of trials to reach 70% of correct responses ≤ 20, $n = 15$) and slow melodic learners (minimum amount of trials to reach 70% of correct responses > 20, $n = 9$). Then, we performed a two-sample t-test in order to compare these two groups regarding their WM microstructure in the dissected pathways. Not surprisingly, we found that these two groups showed a specific significant difference in their mean right AF volume (mean right AF volume for fast learners =9.92, SD = 2.73; mean right AF volume for slow learners = 5.98, SD = 1.87; $t(22) = 3.81$, $p < 0,001$) and FA (mean right AF FA for fast learners = 1.24, SD = 0.21; mean right AF FA for slow learners = 1.02, SD = 0.2, $t(22) = 2.53$, $p < 0.05$).

5.3.3.2 <u>Correlations between music learning and segments of the AF</u>

Within the AF rami, different correlations were found. Concretely, (i) FA in the right long segment was negatively correlated with minimum number of trials needed to reach 70% correct responses in the melody task ($r = -0.42$, $p < 0.05$); (ii) volume in the right anterior segment was positively correlated with learning rate of mASY ($r = 0.55$, $p < 0.001$); and (iii) FA in the right posterior segment was negatively correlated with the grand average of ITI-deviation ($r = -0.35$, $p < 0.05$). In other words: (i) the better the microstructural organization of the right long segment, the faster will be the learning of melodies in the piano; (ii) the greater the volume of the right anterior segment, the greater would be the learning rate for mASY; (iii) the better the microstructural organization of the right posterior segment, the smaller would be the differences between subjects' internal rhythmic pattern and the external model.

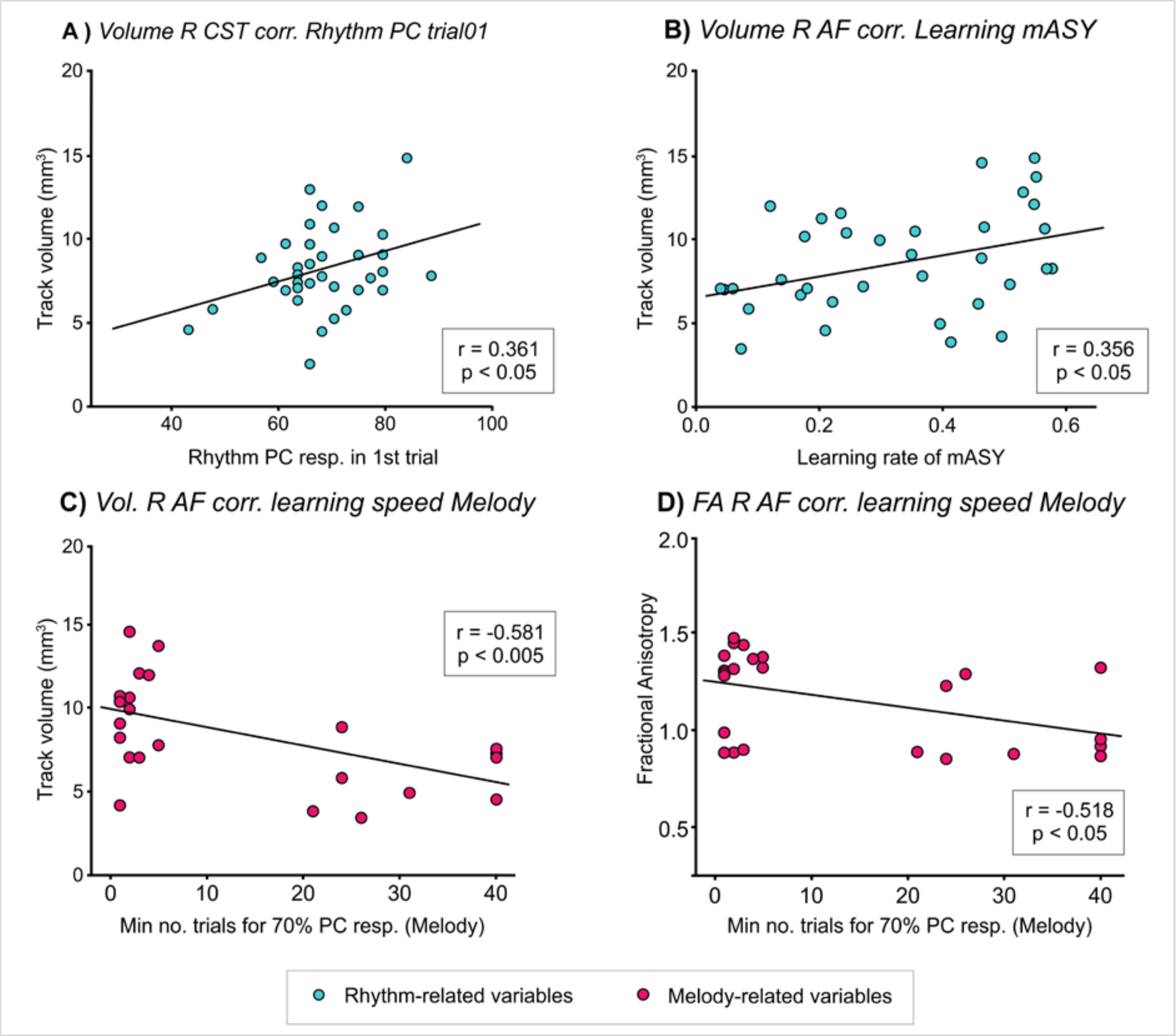

Figure 5.5. Scatterplots showing the significant correlations found between DTI measurements and the performance in the musical tasks. Blue dots correspond to rhythm variables, pink dots show melody-related measures. A) Positive correlation between volume of the right CST and the initial performance in the rhythm task, by means of the percentage correct responses. B) Negative correlation between volume in the right AF and the final performance in the rhythm task, regarding the mean absolute values of asynchrony. C) Positive correlation between volume in the right AF and improvement in the values of mean asynchrony. D) Negative correlation between the volume of the right AF and the learning speed in the melody task (by means of the minimum number of trials needed to achieve 70% of correct responses). E) Negative correlation between FA in the right AF and the learning speed in the melody task. Abbreviations: CST: corticospinal tract; AF: arcuate fasciculus; Rhythm PC T01: percentage correct in the first trial of the rhythm task; mASY T12: absolute mean asynchrony values in the last trial of the rhythm task; TasaLE mASY: learning in mean asynchrony; Vol.: volume; FA: fractional anisotropy.

5.4 Discussion

In the present investigation, we studied for the first time to our knowledge the brain structural substrates predicting musical abilities as well as the individual differences underlying FML in non-musician participants. We gathered structural neuroimaging data from 44 healthy participants before they performed both a rhythm synchronization task and a melody-learning task during a single behavioural experimental session. We correlated the volume and FA values of the arcuate fasciculus (AF) and the corticospinal tract (CST) with the performance and learning parameters obtained in both musical tasks. Our results showed a clear rightward asymmetry with (i) the volume of the right CST predicting correct behavioural performance in the early stages of rhythmic sequences learning and, (ii) the volume of the right AF predicting the learning rate of synchronization, and both the volume and the FA of the right AF predicting the speed of melody learning. Importantly, we also observed different contributions of each segment of the AF: FA in the right long segment predicted learning speed in the melody task while the volume in the right anterior segment predicted the improvement in synchronization performance. Finally, FA in the posterior segment was involved in the adjustment of the internal tapping-pattern to the rhythmic model (grand average of ITI-deviation).

Previous studies exploring the possible prediction of behavioural outcomes from baseline brain connectivity measurements in the auditory-motor domain have reported interesting results. For instance, Ventura-Campos and colleagues (2013) found that pre-training resting-state functional-connectivity between left superior parietal lobe and left frontal operculum/anterior insula predicted the ability for foreign-language phonetic learning, regardless of the length of the training (either 2 weeks or 1 hour of phonetic training). As an example using more music-related material, Zatorre and collaborators (2012) trained individuals to discriminate tonal patterns using microtonal pitch intervals, taking advantage of the parametric response of the auditory cortices, that allows the calculation of the slope of the function relating activity to pitch change. These authors found that those participants who learned more quickly during the 2-week training, showed steeper pitch-change-activation functions before the start of the training (Zatorre et al., 2012). Previous studies (Reiterer et al., 2011, Ventura-Campos et al., 2013) have suggested that brain activity measured during in-scanner tasks or using resting-state functional connectivity measurements may be related to anatomical WM pathways. Actually, López-Barroso et al., (2013) reported that performance in a word-learning/segmentation task significantly correlated both with the WM microstructure of the left long segment of the AF and with the functional-connectivity strength between left temporal and inferior frontal regions. Recent reports have also used electrophysiological measures at baseline to predict performance in second language acquisition paradigms. For example, Qi and colleagues (2016) related variation in electrophysiology (electroencephalographic measures or EEG) during native language processing with successful learning of Mandarin in native English speakers. These authors found that an index of sensitivity to structural regularity (the early P600, which appears mostly in centro-parietal regions, Kaan & Swab, 2003) predicted individuals' learning of novel morphosyntactic rules, while an index of the attempt to access semantic information (the N400, which source is described to be located in the left posterior temporal cortex) was more generally related to successful learning, specifically predicting vocabulary learning (Qi et al., 2016).

In humans and other primates, the CST encompasses the fibres descending from the sensorimotor and premotor cortices (Bengtsson et al., 2005; Cheeran et al., 2009). Previous DTI and VBM studies comparing musicians to non-musicians with cross-sectional designs reported different microstructural patterns of FA modulations in the CST (Schmithorst & Wilke, 2002; Bengtsson et al., 2005; Imfeld et al., 2009). Recent music-training studies with non-musicians have shown that FA in the CST bilaterally predicts melody-learning rates thus suggesting the involvement of the CST in music skills and learning (Engel et al., 2014). Besides, functional imaging studies have observed a clear sensorimotor synchronization network in both musicians and non-musicians, comprising: the primary motor areas, SMA, premotor cortex (both ventral and dorsal), basal ganglia, dorsolateral prefrontal cortex, IFG and cerebellum (Chen et al., 2006, 2008a, b, 2009; Grahn, 2012; for a review see Repp & Su, 2013). Some of these regions receive projections from the CST (mainly, primary motor and premotor cortices). Our results clearly showed that individual differences in this WM bundle were associated to rhythm synchronization learning.

However, we only found that the greater the volume in the right CST, the higher the percentage correct of responses at the very first trial of the rhythm synchronization task (no significant relationship arose from the comparison with the melody-learning parameters). The microstructural organization of WM fibre-tracts on the right hemisphere have been previously related to initial stages of auditory-motor learning (i.e., native English speakers learning Mandarin or native Chinese speakers learning English) (Mamiya et al., 2016; Qi et al., 2015). However, since our participants were exclusively right-handed, this finding may be rather surprising, even more when considering that both the rhythm and the melody learning tasks were performed with the right hand on a PC-mouse or on the keyboard, respectively. Nonetheless, right-greater-than-left lateralization regarding the microstructural organization of the CST has been previously reported, both in musicians and non-musicians (Imfeld et al., 2009; Kraus et al., 2007; Toosy et al., 2003), and the reflection of handedness in the microstructural organization of WM in the CST has been debated and remains an open issue (Imfeld et al., 2009). Bengtsson and colleagues (2005) also found that the right CST showed significant differences between musicians and non-musicians with the number of hours of piano practice during childhood predicting FA values in this area. Taken together, these data suggest that the right CST might be a key structure for music-related functions and learning.

Regarding the other important result, the association between microstructural organization of the right AF and the success in rhythm synchronization and melody learning tasks, these findings are in line with previous reports showing that the left AF is involved in auditory-motor transformations in speech (López-Barroso et al., 2013; Vaquero et al., 2016), while the right AF might be involved in pitch and melodic processing (Albouy et al., 2013; Loui et al., 2011). However, based on previous reports (that break the exclusive left-lateralization for language processing and assign a role of the right AF for some linguistic functions, Paulmann, 2016; Sammler et al., 2015), this fibre bundle is thought to be crucial for audio-motor interactions in both hemispheres. Specifically, the AF is creating a feedback-feedforward loop in charge of accurate perception of auditory stimuli (superior temporal regions), creation of predictions and storage of auditory-to-motor templates (posterior part of superior temporal and IFG), planning of motor actions relevant for the synchronization of audio-motor information (premotor, inferior and middle frontal regions), covert monitoring of motor output as well as comparing current outputs with stored templates (superior temporal and inferior parietal areas), and execution of motor corrections when needed (premotor and IFG) (Cunillera et al., 2009; López-Barroso et al., 2013, 2015; Rauschecker & Scott, 2009; Rauschecker, 2012; Rodríguez-Fornells et al., 2009; Vaquero et al., 2016; Warren et al., 2005; Zatorre et al., 1992).

Due to the cortical areas that the AF interconnects, the functions attributed to them, and the crucial communicating role of the AF in this prediction-feedback-feedforward system, the involvement of the right AF in music learning may not be surprising. As explained above, the right auditory cortex and IFG have been previously related to pitch, speech-contour and melodic processing (Albouy et al., 2013; Coffey et al., 2016; Johnsrude et al., 2000, 2002; Herholz et al., 2015; Hyde et al., 2006, 2007; Zatorre et al., 2002, 2007). Moreover, previous reports focused on professional musicians and/or in comparisons between musicians and non-musicians have also identified the AF as a crucial structure for music abilities (Bengtsson et al., 2005; Oechslin et al., 2010).

Finally, a very recent study shows that the AF is related to rhythm synchronization abilities in non-musicians (Blecher et al., 2016). Specifically, non-musician participants were evaluated in their ability to tap in synchrony with a model and to resynchronize when the external rhythmic pattern changed, correlating these behavioural measurements with DTI information. These authors found that higher FA values in a cluster within the left AF were related to more synchronized tapping to the model (smaller absolute asynchrony). These authors propose that connections through the left AF may be involved in ongoing comparisons between the tapping that is being performed and the auditory stimuli serving as a model, allowing an effective synchronization (Blecher et al., 2016). Although they did not find any significant results on the right AF, they acknowledge that potential limitations of the applied techniques could explain the absence of an (otherwise expected) effect on the right hemisphere (Blecher et al., 2016). In addition, better microstructural organization of the right AF (SLF) by means of higher FA has also been recently related to faster learning rates in a piano-melody learning task (Engel et al., 2014).

Although in light of the present findings it is possible to argue about a possible lack of specificity showed by the AF in music abilities (since it seems to underlie learning in both melodic and rhythmic domains), previous research has also suggested a domain-general involvement of the right AF in activities requiring matching sounds with actions, independent on whether these actions are articulatory or hand movements (Halwani et al., 2011). Thus, it could also be the case that the right AF is involved in general audio-motor integration functions, regardless of the type of task or the music-aspect (i.e., rhythmic, melodic) involved in the task. Furthermore, in regard to the functions associated to each branch of the AF, the long (direct) segment has been related to phonological functions (such as language repetition), while the indirect branches have been associated to lexico-semantic processing (specifically, the anterior segment is thought to be recruited for vocalization of semantic content, and the posterior segment seems to be involved in auditory semantic comprehension) (Berthier et al., 2012; Catani et al., 2005; Dick & Tremblay, 2012). However, these functional correspondence has been mainly described for the left AF and, currently, there is not a clear consensus either regarding the anatomical division of the AF, or the functions associated to each of these segments (Bozkurt et al., 2016; Dick & Tremblay, 2012; Fernández-Miranda et al., 2015; Petrides et al., 2012; Wang et al., 2016).

Despite this lack of consensus, a crucial role of the anterior segment of the AF for auditory-motor learning may be hypothesized based on recent results. For instance, using resting-state quantitative-EEG (qEEG) data before participants underwent 8 weeks of an immersive, virtual scenario of French exposure, Prat and collaborators (2016) found that qEEG indices (i.e., beta and lower-gamma) over right temporo-parietal regions predicted up to 60% of the variability in the final language level achieved by the participants, and that more lateralized distributions of alpha power to the right correlated with faster language learning. This right-lateralized findings are in line with a recent WM structural study (Qi et al., 2015) in which greater initial FA values in the parietal bundle of the right SLF (in other words, the anterior segment of the AF) predicted more successful learning of Mandarin in native English speakers, which is explained by the tonal nature of Mandarin speech. Moreover, as commented above, musicians' research has shown that the right AF (SLF) is one of the WM substrates displaying neuroplastic effects induced by long-term music practice (Bengtsson et al., 2005; Engel et al., 2014; Oechslin et al., 2010).

In humans, fibre tracts continue to mature at least until age 30, with regional differences underlying behavioural development (Bengtsson et al., 2005). Previous literature in brain plasticity suggests that training and learning new skills can induce WM plasticity if it occurs in a period when the involved fibre tracts are still under maturation (Bengtsson et al., 2005; Steele et al., 2013). Genetic factors can affect both the AF and CST systems during development, neurodegeneration and aging, as well as during learning and skill acquisition (Cheeran et al., 2009; Chiang et al., 2011; Jin et al., 2011; Oechslin et al., 2010). For instance, there are particular polymorphisms (i.e., val66met of the brain-derived neurotrophic factor gene) that may affect synaptic plasticity within the CST, reducing the neuroplastic effects derived from motor practice and stimulation (Egan et al., 2013; Hariri et al., 2003; Kleim et al., 2006; Stefan et al., 2000; Wolters et al., 2003; Siebner et al., 2004). Polymorphisms in the COMT (Cathechol-O-MethylTransferase)-gene have also been reported to influence diffusivity measures in the SLF (AF) when related to second language learning (Mamiya et al., 2016). Furthermore, different contributions of environmental and genetic factors have been described to influence the three rami of the AF, with the long segment maturing early (left lateralization) and being mostly affected by shared environmental or familial factors, the anterior branch being lateralized to the right before adolescence and being determined to a similar degree by familial and pure environmental factors, and the posterior segment being the most affected by pure environmental factors (specially on the right hemisphere) (Budisavljevic et al., 2015).

5.4.1 Limitations

We must acknowledge that the present study have some limitations that should take into account in order to make a proper interpretation of the results. Firstly, some problems regarding the DTI data and the melody task were encountered during the recruitment and the testing, which has caused that the final sample for the behavioural rhythm task, does not correspond entirely to the one finally used for the behavioural melody-learning analysis, or for the DTI correlations. This issue prevents us from extracting categorical conclusions regarding the specificity of the dissected pathways (CST, AF) for both musical tasks (only when the same brain data could be compared to performance in both tasks for the exactly same participants, could one be able to draw a clearer conclusion).

Moreover, deterministic tractography and manual dissection methods are accompanied by the often discussed issue of ‘crossing fibres’, as well as the potential bias introduced by the examiner performing the dissections. A frequent systematic error in the DTI modelling process is the inadequacy of the tensor model to characterize fibre orientation when there is more than one fibre population within a voxel, and in which the Gaussian tensor model assumes the principal eigenvector as the only fibre orientation in the voxel (Jones, 2008). Although some solutions have been described and applied in the last years to overcome it, these new methods (i.e. spherical harmonic decomposition, Q-ball imaging, etc.) usually need more processing time and higher resolution images than the ones available for the present study (Jones, 2008; Salat et al., 2009; Seunarine & Alexander, 2009). On the other hand, manual reconstruction of DTI-tracts could be accompanied by an examiner bias. However, we believe that, despite the confounding criteria of different ‘dissectors’ that might influence the analysis and hardened the replication across different DTI-manual reconstruction studies, this method grants an adaptation to the individual anatomy of the tested cohort that could be crucial in the investigation of inter-individual differences.

Finally, we must acknowledge that, despite the fact that we controlled for hours of music lessons and, thus, for our participants’ musical background, we did not control whether our participants have been involved in other regular and long-term trainings or practice in other domains (such as sports, dancing, video-games, or L2-trainings) that could have affected their WM anatomy via neuroplasticity phenomena, and that may have had a transfer-effect on their abilities to music processing and learning.

5.5 Conclusion

Our results confirm that CST and AF WM pathways are crucial for both music learning and individual differences in musical abilities. Although the present work cannot clearly disentangle whether genetic or environmental factors have driven the structural and behavioural variability observed, we can certainly affirm that WM microstructural organization measurements allow us to observe brain anatomical variations paralleling the inter-individual differences in performance (in music-related tasks, in the current case).

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Chapter 6 - General discussion

Language and music are two of the most fascinating activities in the human cognitive repertoire, encompassing a great amount of basic and higher-cognitive abilities, from motor control and auditory perception, to emotional and attention-related processes (Fitch, 2010; Koelsch, 2014; Schön et al., 2010; Zatorre, 2013). Important differences between individuals have been described for both musical and linguistic abilities that may be explained by the underlying brain anatomy. Nonetheless, phenotypes (such as the brain structure) are not a fixed package of characteristics. As a matter of fact, research in the last century has granted the discovery of a more malleable neural system than it was previously thought (Zatorre, 2013). Furthermore, we are also aware of phenomena such as epigenetics, which is helping us to understand the mechanisms through which the environment could change our brain, and how those changes could not only influence our system, but also be transmitted to the next generation (Kolb & Muhammad, 2014; Zatorre, 2013).

Specific environments, learning programs and activities experienced during our lifetime may change our brain structures and functions, but might also be selected based on and driven by our genetic and epigenetic predispositions, in order to match our innate abilities (Scarr & McCartney, 1983). Hence, individual differences are probably the result of genetic, epigenetic and neuroplastic mechanisms interacting in the brain, especially during development. While I was interested in brain plasticity mechanisms induced by professional musical expertise and the potential effects of starting the music training during early developmental stages (Study I), the two remaining studies were dedicated to the study of brain predispositions before any specific training has taken place. Therefore, Studies II and III investigated the neural substrates that may predict individual differences in linguistic (Study II) and musical (Study III) performance in musically naïve subjects.

To do so, two types of structural neuroimaging analyses have been applied to MRI data: cortical and subcortical grey matter volumes were studied using voxel-based morphometry of T1-weighted data, while white-matter pathways were reconstructed using different deterministic analyses on diffusion-weighted images. Although a detailed discussion for each specific experiment can be found at the end of each experimental section (chapters 3, 4 and 5), in this chapter I summarize the main findings of this work, discussing them first in terms of the different aims of this dissertation, and commenting as well how they contribute to the field. I then present the implications of this work, and finish by explaining some of the limitations of the present studies as well as some directions for future research.

6.1 Musical-experience-induced neuroplasticity

6.1.1 Brain structural differences between professional pianists and non-musicians

The first aim of this dissertation was to compare neuroanatomical characteristics between professional musicians and non-musicians. Results from Study I showed differences between these two groups in several brain regions. However, the findings of this study were not exactly fitting our predictions and were not exactly in line with the majority of previous reports. Indeed, an increase in grey matter volume in expert musicians as compared to amateur-musicians and non-musicians has usually been observed (Bermudez et al., 2009; Gaser & Schlaugh, 2003; Schneider et al., 2002, 2005a; Schneider, Sluming, Roberts, Bleeck & Rupp, 2005b). Nonetheless, Study I showed a more complex pattern of results. Compared to non-musician controls, musicians presented increased grey matter volume in areas such as bilateral putamen (related to sequence and reinforcement learning, as well as skill automaticity, Carlson, 2012; Graybiel, 2005; Packard & Knowlton, 2002; Poldrack et al., 2005), hippocampus and amygdala (involved in emotion learning, memory consolidation, novelty detection or pitch detection, among other functions, Amunts et al., 2005; Blair, Schafe, Bauer, Rodrigues & LeDoux, 2001; Koelsch, Fritz & Schlaug, 2008; Koelsch, 2014; Simó et al., 2015; Strange, Witter, Lein & Moser, 2014), right thalamus (acting as a cortical-subcortical interconnectivity hub, Sherman, 2006), bilateral lingual gyri (related to visual and visuo-spatial processing and global shape processing during reading, Mechelli, Humphreys, Mayall, Olson & Price, 2000), and left superior temporal cortex (processing rapid temporal changes in auditory streams, Schneider et al., 2005b; Zatorre, 2013). At the same time, a rightward cluster covering superior temporal regions (auditory cortex on the right, related to pitch and music processing, Zatorre et al., 2002, 2007), postcentral gyrus (sensorimotor control, Kaas, 2004) and supramarginal gyrus (involved in multisensory integration –Carlson, 2012–, language processing –Catani & Mesulam, 2008–, and music-score reading –Besson & Schön, 2001; McDonald, 2006; Stewart et al., 2003–) showed decreased grey matter in musicians as compared to non-musician participants.

These findings seem to point out to differences in the time courses of plasticity-mechanisms or to different effects triggered by music practice depending on the brain region studied. Some areas showed the classic increase in GM, while others presented an unexpected reduction in GM. All these modulations may be seen as the consequences of an efficiency-improvement process induced by sustained active music practice, which may favour synaptic plasticity and synaptogenesis in some regions, and promote pruning-like and efficiency-reduction mechanisms in other areas (Herholz & Zatorre, 2012; Poldrack et al., 2005; Rypma & Prabhakaran, 2009).

6.1.2 Investigating the potential effects of age of acquisition of musical training

In Study I we were also interested in the effect that learning to play an instrument early in life may have on the developing brain. In other words, we wanted to investigate possible neuroplastic effects instantiated in the brain during the sensitive period (from birth until the "somewhat artificial" cut-off set at 7 years of age). In order to do so, we divided the entire group of pianists into two groups based on their age of onset of piano training, while controlling for age at testing as well as for their hours of current and past practice.

We found that early onset of music (piano) practice was related to both reduced GM volume in the right putamen and better temporal precision during scale playing on a piano-keyboard. This is in line with previous findings (Granert et al., 2011; James et al., 2014) showing that reduced volume of GM in the putamen is related to higher piano skills and earlier commencement of music practice. This difference between early- and late-trained pianists may probably be due to optimization processes such as pruning or concise synapsing as a result of extensive practice during sensitive periods.

This is the first time to our knowledge that a well-controlled, well-selected homogeneous sample of instrumentalists is investigated for brain structural organization and music skills, observing effects derived both from long-term music practice and from acquisition of piano training during putative sensitive periods. The complex pattern of structural results observed here challenges the usual view previously, consistenly reported. Our results, in combination with previous findings going in the same direction (James et al., 2014), may motivate further research in this field, promoting the use of a better control of the instrumental background of the musicians included in the experiment, and a combined approach applying both brain anatomical and behavioural data.

6.2 White matter microstructure explaining individual differences in auditory-motor abilities

6.2.1 Volume of the Arcuate Fasciculus predicts foreign-language imitation skills

Study II aimed to test whether the microstructural organization of white matter (volume and/or FA) could predict participants' level of performance in a linguistic task. Specifically, we decided to dissect the arcuate fasciculus (AF), a white-matter bundle previously described to be involved in speech segmentation and language learning (Catani et al., 2007; López-Barroso et al., 2013; Ripollés et al., 2014). We then extracted the volume and FA from the reconstructed AF, and correlated them with the level of performance in a foreign (new) language imitation task. In line with previous studies (Catani et al., 2005; López-Barroso et al., 2013; Zatorre et al., 2013), we found that white matter microstructural markers of the AF predicted the individual behavioural differences observed in the Hindi imitation task.

Interestingly, our results showed a bias in the lateralization of the volume of the AF toward the left hemisphere, implying that a more left lateralized AF is associated with better scores in the Hindi imitation task. This finding is not surprising since our task required the accurate perception of linguistic sounds together with a fast mapping of the new sounds with a precise motor representation of where and how in the oral cavity these sounds are produced. Our results are in line with previous research showing an advantageous role of the left auditory regions in speech and phonetic perception (Zatorre et al., 2002). Moreover, an overspread left-lateralization for linguistic processing has also been described in the literature (although variability among individuals has been reported, Catani et al., 2007, and right-hemisphere regions have been also described to play a crucial role in linguistic functions, Besson et al., 2011; Paulmann, 2016).

However, we were also curious on whether the strategy of the participants would have been to pay attention to prosodic cues. Since they were naïve to these stimuli, they may have processed them as complex non-linguistic acoustic streams. If that would have been the case, a right-hemisphere involvement would have been observed (Sammler et al., 2015; Sihvonen et al., 2016). In contrast, our results point out to a greater implication of the left hemisphere, which may thus indicate that participants were engaging the segmentation and phonetic perceptive mechanisms that they would normally use when exposed to a new language in a "real life" situation, engaging a brain network that it is already tuned to perform this type of audio-motor integration and feedback monitoring in the mother tongue (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009; López-Barroso et al., 2013, 2015).

As a secondary objective, Study II aimed to ascertain whether an automatic method, based on both deterministic and probabilistic/atlas-based information, would show similar results as the manual-deterministic reconstruction of the AF. This was indeed confirmed: white-matter miscrostructural organization in the AF of the left-hemisphere was significantly correlated with Hindi imitation performance using this automatic method (AFQ, Yeatmann et al., 2012). In addition, this approach allowed us to divide the AF in 100 nodes, exploring the FA values in each of those nodes and pointing out to a specific cluster of nodes (region) within the AF that was specially correlated with our behavioural variable. Specifically, we found that a region in the anterior half of the AF that may lie under pre- and postcentral gyri, before the anterior part of the bundle reaches the IFG/Broca's area, is the part of the AF that correlates the most with performance in the Hindi imitation task (only in the left AF). However, the lack of knowledge about the biological translation to neuroimaging/DTI findings, research examples applying this automatic method (AFQ), comparisons between DTI and post-mortem data, and about diffusivity variations inside the same tract, prevent us to interpret the specific meaning of this finding. This region may have projections to the pre- and postcentral gyri, possibly indicating that sensorimotor processing is crucial in language imitation, but it could also be the case that integrity in that concrete part of the tract may be a marker of the integrity along the whole path; in any case, this is still speculative.

In summary, results from Study II confirmed the crucial role of the left AF in speech perception and articulation. We have used a more ecological approach than previous language imitation/repetition paradigms, combining as well the advatages of two different tractography methods to explore the diffusion data.

6.2.2 White-matter pathways previously reported to be modified by long-term music experience are involved in the first stages of music learning

Study III aimed to investigate the relationship between the WM structural connectivity and the inter-individual differences in music learning skills of non-musician participants, assessed via a fast music learning paradigm (i.e., performed in a single session). We have observed a right-bias in WM microstructural organization related to musical skills. On the one hand, the right CST seems to be crucial for an accurate initial performance of rhythm sequences. On the other hand, the right AF appears to be involved both in synchronization abilities in a rhythm task and in learning to play a melody on a piano. Furthermore, within the AF, each segment was observed to correlate with different musical traits: the right long segment was related to the speed of learning for playing melodies in the piano, the right anterior segment predicted the improvement in synchronization abilities in the rhythm task, and the right posterior segment seems to be in charge of the adaptation of the internal rhythmic pattern to the external model.

Both genetic and environmental factors are thought to influence the individual variability observed in WM microstructural organization and connectivity. As a matter of fact, certain polymorphisms have been reported to influence the diffusivity measures and the synaptic plasticity mechanisms within the CST and the AF (Egan et al., 2013; Hariri et al., 2003; Kleim et al., 2006; Mamiya et al., 2016). But previous reports have also described plastic effects elicited by long-term music practice on the CST and the AF (Bengtsson et al., 2005; Engel et al., 2014; Oechslin et al., 2010).

In the present work we have confirmed the important role of the CST and the AF in music skills and initial stages of music learning, when sustained music-practice is ruled out. Interestingly, the right AF appears as a crucial structure both for rhythm synchronization and for melodic learning abilities, which is in line with previous results evidencing the involvement of the cortical areas it connects in pitch and music processing (Albouy et al., 2013; Coffey et al., 2016; Herholz et al., 2015; Hyde, Zatorre, Griffiths, Lerch & Peretz, 2006; Hyde et al., 2007). Furthermore, we suggest that the right anterior segment would be the crucial portion of the AF in music-related activities and learning, due to its natural right lateralization established early in life (Budisavljevic et al., 2015), as well as to the present findings and previous functional and structural research that have implied an important relationship between this fronto-parietal connection and learning in the auditory-motor domain (such as second language learning) (Prat et al., 2016; Qi et al., 2015).

Although the white-matter microstructural organization has predicted individual differences in music performance in our participants, it is not possible at this moment to disentangle the contribution of the genetic, the environmental or the combined effect of both nature/nurture factors in shaping the specific brain wiring required during the learning of these musical tasks.

Study III explored for the first time to our knowledge the white-matter connectivity correlates of music learning abilities by using a manual-deterministic approach (instead of the voxel-based analyses or probabilistic tractography approiaches previously applied) and measuring both rhythm synchronization and melodic learning skills in non-musicians during a single training session (fast music learning paradigm).

6.2.3 White-matter microstructural organization: a predisposing factor or a scaffold for neuroplasticity?

White matter microstructure has been largely reported to be modifiable by experience (Johansen-Berg et al., 2012; Sagi et al., 2012; Zatorre et al., 2012; for a review see Zatorre et al., 2013). In particular, auditory-motor training has been reported to trigger neuroplastic phenomena in several WM tracts of the brain (Bengtsson et al., 2005; Halwani et al., 2011; Imfeld et al., 2009; Oechslin et al., 2010; Steele et al., 2013). Nonetheless, recent investigations have also drawn attention to the importance of the initial functional brain connectivity and white-matter structural connectivity, and how these brain individual differences may predict the success of specific trainings and learning (Herholz & Zatorre, 2012; Zatorre, 2013). Moreover, genetic predispositions as well as the maturational stage of the brain could act as boosting factors for the neuroplastic changes associated to experience and learning (Steele et al., 2013; Zatorre, 2013).

In a recent review, Besson, Chobert and Marie (2011) argued that, based on the observations made in longitudinal experiments in which non-experts are trained and exhibit brain functional and structural alterations post-training, the differences reported in the literature between musicians and non-musicians are more likely to result from musical training rather than from genetic predispositions toward music processing and skills. However, only longitudinal studies based on the accurate observation of brain maturation, particular abilities and activity-choices in children could help in disentangling this issue.

At the moment, and regarding our results, we can only propose that differences in white-matter microstructural connectivity could predict inter-individual differences in learning success. Hence, following the most accepted view in the field, one should keep in mind that, most probably, both the genetic background as well as the individual's experiences, have shaped each participant's neural systems and, thus, the individual differences observed should be considered as a combination between innate abilities and neuroplastic modifications fostered by personal experiences (Gilliam et al., 2000; Zatorre et al., 2013).

6.3 Plasticity in musicians vs. predispositions in non-musicians: feedback/feedforward loop observed in different stages of audio-motor learning

Our results for the AF in both Study II and III point out to the important role of an intact feedback-feedforward loop, required to perform an accurate production of speech and musical material. In order to imitate or reproduce new auditory information, the brain relies on WM pathways and cortical regions already specialized in creating an audio-motor model based on predictions, comparing incoming information with the existing templates and monitoring the articulation or motor production in order to plan and execute corrections whenever errors in the predictions are detected (such as the AF, which communicate all this information during language-proccesing in the mother tongue) (Cunillera et al., 2009; López-Barroso et al., 2013, 2015; Rauschecker & Scott, 2009; Rauschecker, 2012; Rodríguez-Fornells et al., 2009). In the present work, non-musicians (and some non-expert musicians) exposed to a new language or new musical material have shown to involve a brain network that corresponds to the dorsal route for language processing and that seems in charge of a mechanism of prediction-feedback-feedforward in the audio-motor domain. Actually, this feedback-feedforward loop for audio-motor productions has been already suggested to play a crucial role in both music and language (Herholz & Zatorre, 2012).

In Study II, participants may have relied on the dorsal route for language on the left hemisphere, the same one that is thought to be used to articulate the sounds of their mother tongue, in order to adapt their oro-motor system for the accurate pronunciation of new phonetical structures (i.e., Hindi words/sentences). In parallel, participants in Study III may have used the right homologous dorsal route to become better synchronized with an external rhythmic pattern. Importantly, non-musician individuals in Study III improved their rhythm synchronization abilities trial by trial. When one starts to play a musical instrument, visual, proprioceptive and auditory feedbacks are crucial. But once the music skills are acquired and mastered, neural systems may undergo a reorganization following the principles of economy, becoming more automatic and less feedback-dependent (Krings et al., 2000; James et al., 2014). For instance, Kleber and colleagues (2013) compared singers with non singers in singing production after vocal-fold anesthesia and discovered that both groups were affected in pitch accuracy, but singers were more able to maintain an in-tune production. This leaded to the conclusion that expertise improves the forward auditory-motor model efficiency, leading to correct productions in the absence of sensory feedback (Kleber et al., 2013). In another fMRI study comparing singers and non-singers, Zarate and Zatorre (2008) asked their participants to sing a single tone while the auditory feedback during production was either maintained unaltered or altered in pitch (and when altered, subjects had trials in which they had to ignore the shift and trials in which they had to compensate for the shifted feedback). In both pitch-shifted tasks, singers outperformed non-singers; however, singers exhibited increased auditory activity as they monitored the auditory feedback, as well as increased activity in the putamen, suggesting that they used well-rehearsed vocal motor programs to complete both pitch-shifted tasks (Zarate & Zatorre, 2008). These changes in automaticity and feedback-dependence may be also evidenced by reductions in activity or tissue, as a consequence of chunking processes and improvements in efficiency on the multisensory-motor pathways that have been observed to be triggered by long-term music training (Herholz & Zatorre, 2012; Poldrack et al., 2005; Rhypma & Prabhakaran, 2009).

Interestingly and in line with these ideas, pianists in Study I presented a reduction of GM volume in the right superior temporal gyrus, right postcentral gyrus and right supramarginal gyrus, all cortical regions connected by the AF and that may be showing a shrinkage of GM volume induced by extensive musical practice. In summary, based on the results of these three studies, we propose that the right AF as well as the cortical regions connected by this WM bundle (mainly temporal, inferior frontal, sensorimotor, inferior parietal areas) are crucially involved in learning auditory stimuli being either linguistic or musical materials. This network may control the creation of auditory-to-motor templates in which predictions are based, the planning of movement sequences to match the predictions, the monitoring of acoustic and somatosensory feedback and the execution of proper motor corrections when errors are detected (feedforward).

Moreover, we believe we have observed this prediction-feedback-feedforward loop in different stages of acoustic learning: greater volume in AF is necessary for the initial steps of language or music production (on the left hemisphere for language imitation functions, Study II, and on the right side for rhythm synchronization and melodic learning, Study III), while smaller volume of GM in the cortical regions interconnected by the AF (i.e., auditory, multisensory integration and somatosensory areas) evidences the refinement or increased efficiency of this brain network through extensive and long-term practice in professional musicians (Study I). Table 6.1 summarizes the results of the present dissertation in regard to the areas involved in this feedback-feedforward loop, showing as well some examples of previous brain-structural research that have observed these same areas as involved in language and music learning.

6.4 Implications

In the last decade, neuroscience research has put a great effort in understanding the neural substrates and processes underlying linguistic and musical activities (Ferreri & Verga, *In Press*; Tillmann, 2012; Zatorre, 2013). Both speech and music are auditory signals than unfold in time, following an internal structure and a particular set of rules that can be learned through mere exposure (Besson et al., 2011; Patel, 2003; Schön et al., 2010; Tillmann, 2012). Recent neuroimaging findings have also revealed that speech and music processing present a large overlap in both brain structures and functions (Besson et al., 2011; Kraus & Chandrasekaran, 2010; Patel, 2003, 2008). Moreover, transfer effects from long-term music practice such as improved perception of speech in noise, enhanced pitch discrimination, or improved speech segmentation have been previously reported (Besson et al., 2011; Bidelman & Krishnan, 2010; Bidelman, Gandour & Krishnan, 2011; François & Schön, 2014).

It has therefore become evident that music can have a social impact that is worth investigating for educational and rehabilitation purposes (for a review, see François et al., 2015). For instance, musicians have been reported to possess better neural encoding of speech sounds, which may help in the extraction of the metrical structure of speech (Port, 2003). Furthermore, musically trained children have been found to ourperform non-musician children in their abilities to segment the syllables in a speech stream (François, Chobert, Besson & Schön, 2013). These examples suggest a beneficial application of music training and musical cues for pedagogical purposes, in order to boost language acquisition and improvement in children. Moreover, these results also point out to the potential benefits of musical-related programs in the rehabilitation of pathological cases in which language functions are impaired. As a matter of fact, music intonation therapy has been effectively applied in aphasic patients (Norton, Zipse, Marchina & Schlaug, 2009; Schlaug, Marchina & Norton, 2009). In addition, the use of rhythmic cues and music training to boost linguistic abilities have been also used in children with language impairments, such as developmental dyslexia (Cason, Hidalgo, Isoard, Roman & Schön, 2015; Cogo-Moreira, de Avila, Ploubidis & de Jesus Mari, 2013; Overy, 2000, 2003). Daily music listening (of self-selected pieces, during 2 months) has also been applied in stroke patients, leading to the observation that this easy administered activity can improve verbal memory and focused attention in those patients (Särkämö et al., 2008.). Finally, regarding more emotion-related processes, music-supported therapy (MST) and music listening have been also reported to improve mood regulation in stroke patients (Ripollés et al., 2015; Särkämö et al., 2008, 2014).

Areas involved in feedback-feedforward loop	*Present results*			*Previous results (brain structure and music learning in non-musicians)*				*Previous results (brain structure, language learning)*			
	Study I	**Study II**	**Study III**	**Foster & Zatorre, 2010**	**Engel et al., 2014**	**Blecher et al., 2016**	**Schlaug et al., 2005**	**Golestani et al., 2002**	**Golestani et al., 2007**	**López-Barroso et al., 2013**	**Qi et al., 2015**
Auditory regions	Increased GMV in L STG, reduced GMV in R STG {in musicians}	Lateralization bias to the L in the volume of the AF predicted foreign-language imitation abilities	Volume of R AF predicted synchronization improvements, Volume & FA of R AF predicted melody-learning speed.	GM concentration & cortical thickness in R HG predicted performance in a melody transposition task	Higher FA in R AF predicted faster learning rates in a piano-melody task	Higher FA in a frontal cluster within the L AF predicted better rhythmic synchronization abilities			Increased WM density in L HG predicted fast phonetic learning	Less RD (better WM microstructural organization) in the L long segment predicted word learning rates	
IFG / middle frontal / insular cortex											Higher FA in the R ant. segment of the AF predicted learning of Mandarin
Primary motor							Instrumentalists had more GM in motor cortex				
Premotor / SMA											
Primary somatosensory	Reduced GMV in R PCG {in musicians}						Instrumentalists had more GM in somatosenory cortex				
Inferior parietal	Reduced GMV in R SMG {in musicians}			GM concentration & cortical thickness in bilateral IPS predicted performance in a melody transposition task				Increased GMV and WMV in L parietal regions predicted learning speed of speech & non-speech sounds			

Table 6.1. Present and previous (only structural) results involving areas connected in the feedback-feedforward loop, in relation to language & music learning. Abbreviations: IFG, inferior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus; GMV, grey-matter volume; WM, white matter; SMG, supramarginal gyrus; PCG, postcentral gyrus; HG, Heschl's gyrus; IPS, intraparietal sulcus; L, left; R, right; AF, arcuate fasciculus; FA, fractional anisotropy; RD, radial diffusivity.

Besides language- and more cognitive-related deficits, music has also proven to be an excellent tool for motor rehabilitation. Music-supported therapy (MST) aims to restore paresis of the upper limb by learning to play a musical instrument (Schneider, Schönle, Altenmüller & Münte, 2007), and has been related to functional changes caused by brain reorganization processes (François et al., 2015). Specifically, Ripollés and colleagues (2015) observed improvements in motor and cognitive functions in chronic stroke patients who underwent one month of MST, as well as a clear restitution of both activity and connectivity among auditory and motor regions of the affected hemisphere. Moreover, transchranial magnetic stimulation (TMS) techniques have shown that motor improvements in the paretic hand of stroke patients are paralleled with changes in cortical excitability in sensorimotor regions (Amengual et al., 2013; Grau-Sánchez et al., 2013). Furthermore, rhythm auditory stimulation (RAS) has proven to be effective in overcoming gait velocity, stride length and step cadence in Parkinson's disease patients (Fernández del Olmo & Cudeiro, 2003; Nombela, Hughes, Owen & Grahn, 2013; Thaut et al., 1996).

Finally, music practice possess a social component (playing and enjoying music are common daily-life activities that are usually shared with other individuals), and both music training and social interaction have shown to facilitate L2 acquisition (Verga & Kotz, 2013). Probably due to both its beneficial effects for language processing as well as for this social component, music training has been observed to be a facilitator for communication and social interaction in autism disorder (Molnar-Szakacs & Heaton, 2012; Overy, 2012).

Based on previous literature, one can confidently claim that music-related activities have a promising potential both for educational and rehabilitative applications. Thus, research focused in improving our understanding regarding music processing, music learning and its associated neural plasticity mechanisms, as well as the cross-domain transfer associated to music practice, can have great implications for the society.

6.5 Limitations & Future directions

We must acknowledge that several factors might have affected the present results and that they should take into consideration when interpreting our findings (this subsection aims to be a rough summary, but see a detailed list of limitations specified in each experimental chapter –3, 4, 5– for particular confounding factors). First of all, structural neuroimaging techniques and analyses possess some limitations, mainly: (i) the difficulties regarding the tissue segmentation during VBM, which may include voxels pertaining to white matter in the grey matter maps or the other way around, specially in small structures (such as the hippocampus or the amygdala) and in the boundary-zones between these two types of tissue (Ashburner, 2010); (ii) the ‘crossing fibres issue’ in deterministic tractography analysis on DTI data, in which the categorization of fibres based on their direction could be impaired due to multiple directionality information inside the same voxels, and which may affect the reconstruction output; (iii) the potential bias that manual dissection of white-matter tracts can include in the analyses, due to the particular criteria used by different examiners across studies, which may limit the extrapolation of conclusions. Besides, as commented in the introduction, the biological meaning of neuroimaging findings remains an open issue, preventing us from drawing any clear conclusion on the specific neural mechanisms underlying our observations at the molecular and cellular levels.

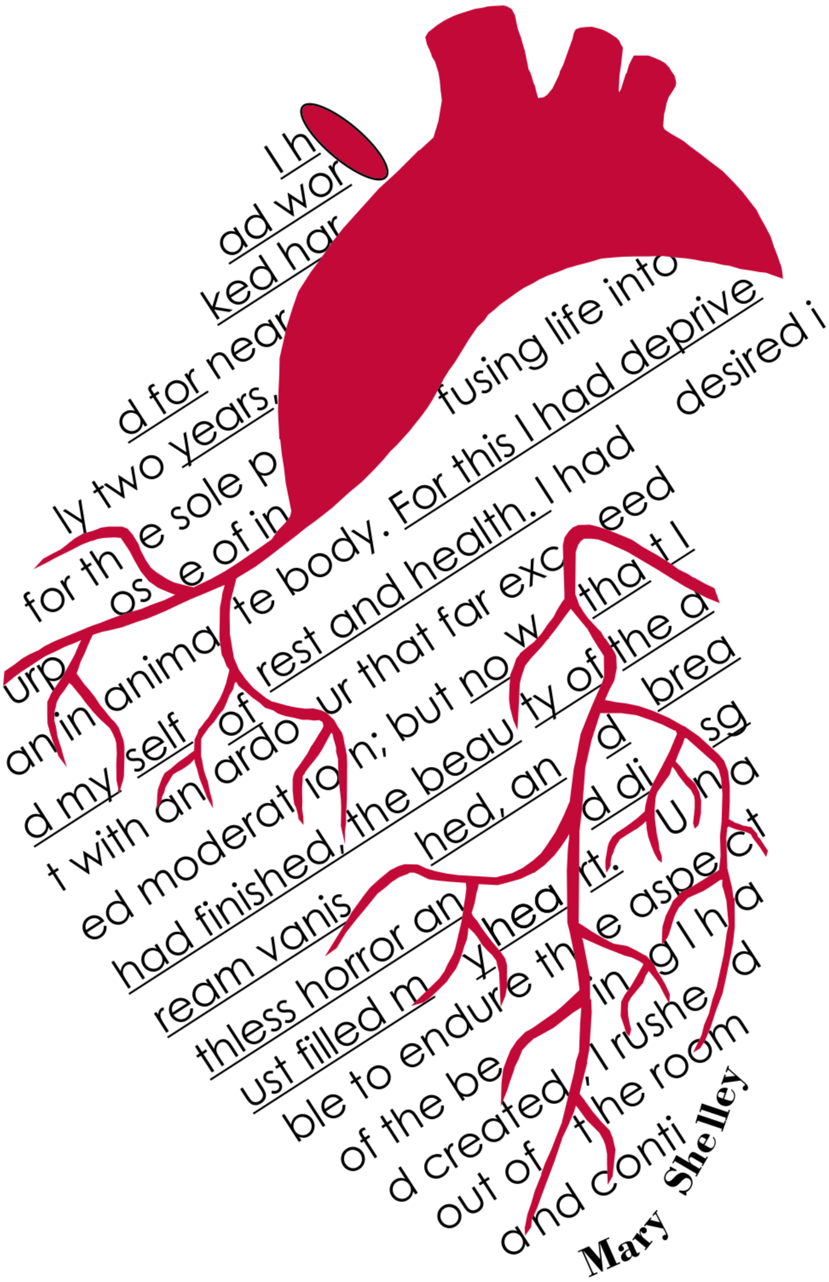
In addition to technique- and analysis-related limitations, we are also aware of several limitations related to the experimental designs and their implementation. In Study I, a larger sample size could have provided us with a more-covered distribution among the early- and late-trained musicians. Indeed, we were not able to include pianist participants with ages of onset covering the range between 9 and 12 years old. In Study II, the measure of imitation was obtained via a composite score based on the ratings of Hindi native subjects on three sentences and one word. Although interesting, these results could be seen as a general measure of foreign-language imitation that could be improved by comparing: (i) imitation of sentences with imitation of words, (ii) language imitation with singing production (see Christiner & Reiterer, 2013), (iii) language imitation with other linguistic tasks such as speech segmentation or prosody perception. In Study III, technical problems both with DTI during imaging acquisition and with the melody learning task in the piano impeded us to gather the rhythm, melodic and neuroimaging data for all the participants, decreasing the statistical power as well as the conclusions that could be drawn (since the number of participants included in the behavioural measures is not the same for both musical tasks, neither for the comparison between musical performance and microstructural organization of white matter tracts). In addition, a more complete record of other non-musical but motor or audio-motor activities performed by participants included in Study III (such as sports or L2 training) could have been useful to control for other types of training that may have affected the brain structure and function of these individuals, imprinting certain characteristics in the ‘white matter predispositions’ measured in the present work.

Regarding possible future directions, the very same data obtained in the three experiments could be explored in different ways, allowing us either to draw a clearer picture or to confirm the conclusions drawn by the results explained above. For instance, in Study I, a specific parcellation of the Hechsl's gyrus or the precentral and postcentral gyri (as done in Schneider et al., 2002, 2005 a, b; Seither-Presiler et al., 2014) could permit a region-of-interest driven approach that could show interesting results at a more local level, both in the comparison between musicians and non-musicians, as well as between early-trained and late-trained pianists. In Study II, as commented above, the division of sentences and word imitation, as well as the inclusion of other language-related tasks tapping different linguistic functions, could make the study far more complete. Furthermore, other WM tracts related to audio-motor functions (such as the frontal aslant tract) or encompassed in the ventral route of language processing (like the IFOF or the uncinate) may also show an important or a lack of involvement in the imitation task that could be informative as well. For Study III, the dissection of other tracts related to audio-motor and emotional functions and, thus, potentially involved in music processing/production (such as the subcallosal tract, the tapetum of the corpus callosum, the cerebellar pathways, or the thalamic projections), could be interesting in order to have a more complete picture of the white-matter structures predicting music skills. Besides, at the time of the data collection, we included a multifeature MMN paradigm while recording the EEG signal (Näätänen, Pakarinen, Rinne & Takegata, 2004; Putkinen, Tervaniemi, Saarikivi, Ojala & Huotilainen, 2014; Vuust et al., 2011, 2012) as well as a behavioural singing task (Christiner & Reiterer, 2013). However, due to the length of the protocol, only a few participants completed those tasks and thus, the re-recruitment of those participants who did not complete the tasks (or of new participants who could complete the full protocol) would be necessary to analyse these data, which on the other hand could add interesting information when compared to the rhythmic-melodic and DTI findings we have at the moment.

Finally, a more general goal for future research could be performing longitudinal studies in children. Longitudinal designs may allow us to track proper predispositions toward both music skills, as well as to confirm whether those children with better audio-motor skills would seek for musical or linguistic activities (in line with proposals by Scarr & McCartney, 1983). This kind of longitudinal studies would allow us to investigate in more detail the effect of age of acquisition of musical training during normal maturation, as well as the traces that early music training can leave in brain structure (and function) when musical practice is disrupted at some point between adolescence and adulthood. Recent cross-sectional studies by Ullén and collaborators (Butkovic, Ullén & Mosing, 2015; Mosing et al., 2014; Mosing, Madison, Pedersen & Ullén, 2015) have challenged the idea that music practice may be the only causal agent for neural and behavioural differences observed underlying music training and skills. These authors suggest that current cross-sectional and longitudinal findings should be interpreted with caution, without rulling out the possible mediation of genetic factors (Mosing et al., 2015). However, in one of the few longitudinal studies with children in which some of the participants enrolled in music-training programs in the curse of the experiment, Schlaug, Norton, Overy and Winner (2005) did not find any pre-existing cognitive, music abilities, motor, or structural brain differences between the musician and the control groups at baseline. This lack of differences led the authors to suggest that it is unlikely that the children who decided to start a musical training have done so due to atypical brain function or structure (Schlaug et al., 2005). This is in line with previous longitudinal research that seem to indicate that the observed differences in relation to musical training are indeed manifestations of experience-dependent plasticity (instead of consecuences of pre-existing variability) (see review by Herholz & Zatorre, 2012).

At the moment, there is not enough evidence to solve the debate as to whether the genetic factors or the environmental-training-related factors explain inter-individual differences in music skills the most. The proposed observational longitudinal studies in children would provide important information to the confounding framework created by more genetic-driven conclusions (Mosing et al., 2014, 2015) as compared to more plasticity-induced observations (Besson et al., 2011; Schlaug et al., 2005) that have led to the currently mixed results.

Chapter 7 - Conclusion



In this dissertation I have combined different approaches to study brain structural imaging (MRI) data with behavioural measurements of music skills and foreign-language imitation. The main goal of the present work was to investigate the neuroanatomical substrates predicting audio-motor performance and abilities, as well as the structures that may display brain plasticity induced by sustained musical practice.

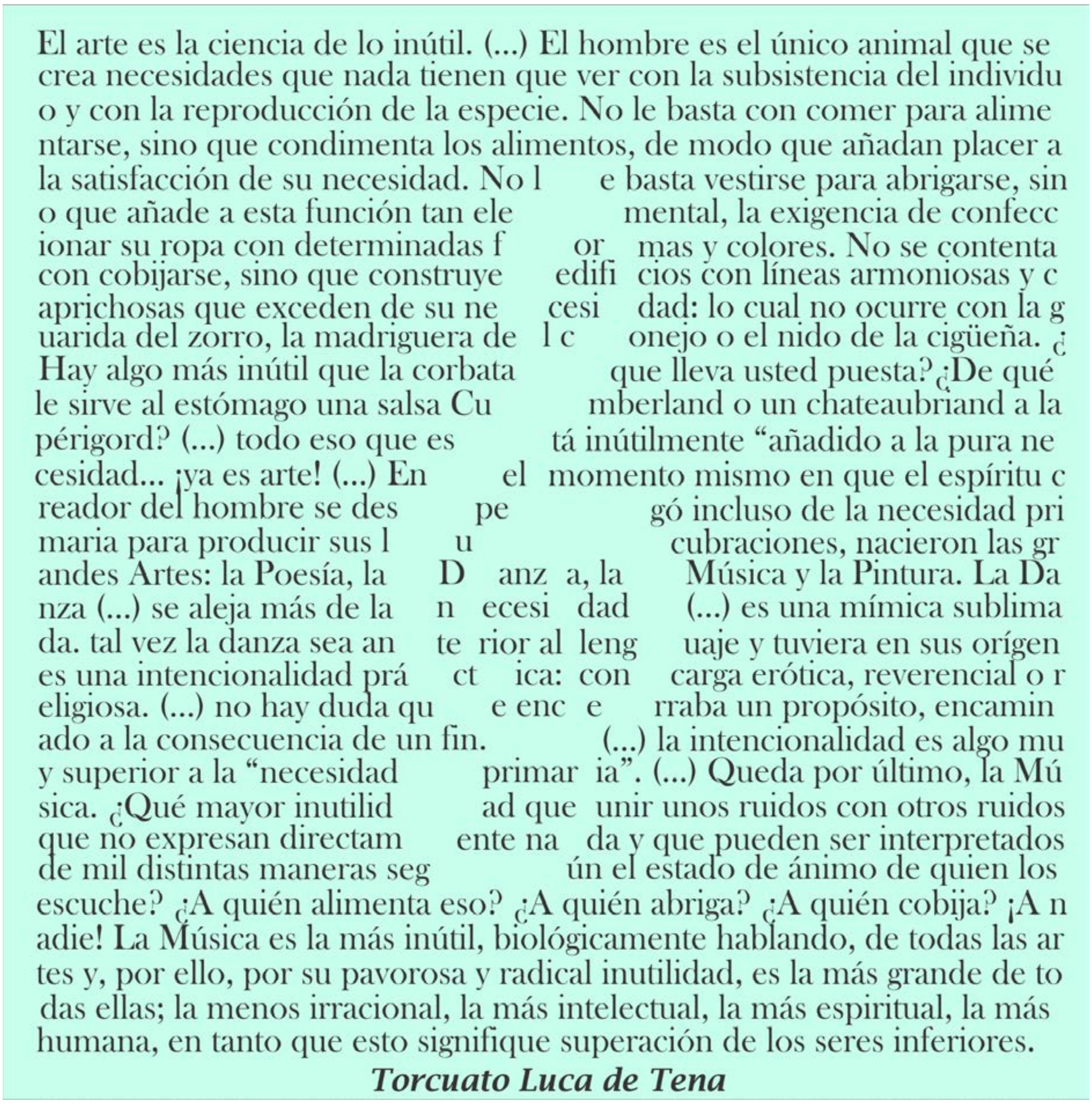
Interestingly, our results have evidenced that brain structural markers can provide interesting clues in regard to learning mechanisms. Specifically, we have observed that the dorsal route described for language processing (Hickok & Poeppel, 2004, 2007) is involved in music as well as in linguistic abilities. Moreover, our data suggest that this network may be a crucial substrate during initial stages of audio-motor learning. In addition, these connected regions may disclose the effects of neural plasticity, possibly underlying a refinement of the neural system triggered by sustained and highly-demanding experiences (such as learning to play a musical instrument at a professional level).

More concretely, we have observed that the variability in the microstructural organization of the arcuate fasciculus (AF) and its lateralization predicted the individual differences in a foreign-language imitation task: a greater lateralization bias in the volume of the AF toward the left hemisphere was associated with a better performance in the language imitation task. Besides, differences in the microstructural organization of the right AF were associated with individuals' performance in musical tasks; specifically, a higher volume in the right AF predicted greater improvements in rhythm synchronization abilities as well as faster learning rates of melodies in the piano. Conversely, a reduction in cortical grey-matter volume in right auditory, somatosensory and multi-sensory integration regions was associated with long-term professional piano practice.

We think the present results have contributed to enlarge our knowledge regarding the mechanisms underlying audio-motor learning processes, supporting previous structural and functional findings that have suggested the involvement of the dorsal-route (for language processing) regions in auditory-motor transformations. In addition, we think the experimental designs used in the present work have controlled and addressed several important issues and questions that remained open in previous research. Specifically, first of all, we performed a more controlled selection of the musician participants (Study I) than previously done, by including only high-level pianists, eliminating thus possible confounds derived from the different plastic mechanisms that may be associated with practicing different instruments (Tervaniemi, 2009). Secondly, we carried out a more ecological task for measuring foreign-language imitation abilities than the previously employed paradigms (Study II). Moreover, we applied two different approaches in the analysis of the brain-structural data (i.e., manual vs. automatic white-matter fibre dissections), which have served us to corroborate the results as well as to overcome some of the possible limitations of using only one of those techniques. Finally, we have investigated two domains of musical abilities (i.e., rhythm and melodic) in a single-session protocol (Study III) that we believe can help in better disentangling the neural basis of music learning and skills. In addition, we have explored brain-structural predicting factors by using manual-deterministic dissections of white-matter fibres, which to the best of our knowledge is the first time that it is performed.

The study of music and linguistic abilities and the investigation of plasticity mechanisms related to experience in both domains, may not only help us researchers to disentangle the neural mechanisms associated with audio-motor learning, but it can also have important applications to social matters. For instance, and as it has been recently reported (François et al., 2015), conclusions derived from studies comparing musicians with non-musicians as well as from music-training paradigms could be applied to educational purposes (for improving memory and linguistic functions) as well as for motor and language rehabilitation (in stroke patients with hemiparesia or with aphasia, for example). Additionally, although it falls outside the scope of the present dissertation, music training has been reported to have important benefits in emotional processing and mood control, as well as in social interaction (which grants a promising use of music-related approaches in psychological and neurological diseases cursing with deficits in these areas, such as stroke or autism-spectrum disorder).

Chapter 8 - Resumen en castellano



El arte es la ciencia de lo inútil. (...) El hombre es el único animal que se crea necesidades que nada tienen que ver con la subsistencia del individuo y con la reproducción de la especie. No le basta con comer para alimentarse, sino que condimenta los alimentos, de modo que añadan placer a la satisfacción de su necesidad. No le basta vestirse para abrigarse, sino que añade a esta función tan elemental, la exigencia de confeccionar su ropa con determinadas formas y colores. No se contenta con cobijarse, sino que construye edificios con líneas armoniosas y caprichosas que exceden de su necesidad: lo cual no ocurre con la guarida del zorro, la madriguera del conejo o el nido de la cigüeña. ¿Hay algo más inútil que la corbata que lleva usted puesta? ¿De qué le sirve al estómago una salsa Cumberland o un chateaubriand a la périgord? (...) todo eso que está inútilmente “añadido a la pura necesidad... ¡ya es arte! (...) En el momento mismo en que el espíritu creador del hombre se despegó incluso de la necesidad primaria para producir sus lucubraciones, nacieron las grandes Artes: la Poesía, la Danza, la Música y la Pintura. La Danza (...) se aleja más de la necesidad (...) es una mímica sublimada. tal vez la danza sea anterior al lenguaje y tuviera en sus orígenes una intencionalidad práctica: con carga erótica, reverencial o religiosa. (...) no hay duda que encerraba un propósito, encaminado a la consecuencia de un fin. (...) la intencionalidad es algo muy superior a la “necesidad primaria”. (...) Queda por último, la Música. ¿Qué mayor inutilidad que unir unos ruidos con otros ruidos que no expresan directamente nada y que pueden ser interpretados de mil distintas maneras según el estado de ánimo de quien los escuche? ¿A quién alimenta eso? ¿A quién abriga? ¿A quién cobija? ¡A nadie! La Música es la más inútil, biológicamente hablando, de todas las artes y, por ello, por su pavorosa y radical inutilidad, es la más grande de todas ellas; la menos irracional, la más intelectual, la más espiritual, la más humana, en tanto que esto signifique superación de los seres inferiores.

Torcuato Luca de Tena

Como miembros de la especie, todos los seres humanos poseemos ciertas predisposiciones generales, como puede ser la capacidad de a aprender la lengua de nuestra comunidad o el hecho de que nuestro cerebro posea unas redes neurales que ya están preparadas para procesar los estímulos musicales desde la infancia (Fitch, 2010; Perani et al., 2010). La carga genética heredada de nuestros padres determina nuestro fenotipo y nuestras habilidades innatas. Además, la herencia genética también puede predisponer a los individuos a buscar ambientes y actividades que se correspondan con sus habilidades innatas. Pero la influencia del ambiente tiene también un papel importante; de hecho, se ha demostrado la existencia de fenómenos neuroplásticos asociados a la experiencia y al aprendizaje (así como también después de una lesión cerebral o un exceso de práctica). Por otra parte, la interacción social también puede reforzar las opciones ambientales que influyen en la maduración del cerebro y que se van llevando a cabo durante el desarrollo normal (Scarr y McCartney, 1983). Siguiendo esta última idea, la interacción social es un aspecto crucial tanto en la formación musical como en la adquisición del lenguaje, tal y como puede apreciarse en ciertas experiencias de la "vida real" (es necesario la interacción entre, al menos, dos personas para establecer cualquier forma de comunicación) y como se ha demostrado en paradigmas de aprendizaje de un segundo idioma y en diferentes procedimientos de rehabilitación (aplicados al autismo, por ejemplo) (Molnar- Szakács y Heaton, 2012; Overy, 2012; Verga y Kotz, 2013).

Según lo descrito hasta la fecha, se piensa que las alteraciones en nuestra estructura cerebral se llevarían a cabo gracias a fenómenos de neuroplasticidad, que pueden o no ser mediados por procesos epigenéticos (formas heredadas de la lectura del material genético, que no alteran la secuencia de ADN). Además, como explicaban Zatorre et al. (2012), el comportamiento es controlado y expresado por el cerebro pero, a su vez, la conducta puede alterar el funcionamiento y la anatomía del cerebro, modificando y adaptando la estructura cerebral en paralelo al entrenamiento que se esté realizando o a las demandas ambientales (Pascual-Leone, 2001). En la figura 1.14 de la introducción se puede encontrar una visión esquemática de las ideas explicadas aquí.

El objetivo principal de esta tesis doctoral es estudiar los sustratos anatómicos que subyacen a las predisposiciones lingüísticas y musicales en sujetos sanos, así como los efectos relacionados con la neuroplasticidad inducida por entrenamientos mantenidos en el tiempo y con la edad de inicio de la práctica musical. Los procesamientos musical y lingüístico están estrechamente entrelazados en el cerebro humano y las funciones que determinan estas dos actividades se superponen, en gran medida, en varias regiones cerebrales (Patel, 2003; Schön et al., 2010; Tillmann, 2012). Tanto la música como el lenguaje necesitan fragmentar o segmentar los estímulos auditivos largos en unidades individuales más simples (Tillmann, 2012); las dos actividades contienen componentes rítmicos y melódicos (Tillmann, 2012; Zatorre et al., 2007); implican una estructura definida y contienen unas reglas que se pueden extraer por mera exposición (es decir, la sintaxis, Patel, 2003; Patel et al., 2008; Tillmann et al, 2000); poseen un significado asociado (es decir, la semántica, Koelsch et al., 2005a; Patel, 2003); así como un contenido emocional con importantes contribuciones al mensaje general (Paulmann, 2016; Salimpoor et al., 2013).

Tanto la música como el lenguaje implican la percepción de secuencias auditivas complejas; la planificación y la reproducción motoras para ejecutar expresiones verbales, cantar o tocar un instrumento; y un bucle de retro-alimentación (*feedback*) y de alimentación directa (*feedforward*) encargado de la integración en tiempo real de la producción verbal/musical, así como de la comparación de la ejecución que se está llevando a cabo con las representaciones almacenadas previamente, permitiendo así la corrección de los patrones motores en el caso de que se detecten errores (Kleber et al., 2013; Rauschecker y Scott, 2009; Rauschecker, 2012; Warren et al., 2005; Zarate, 2013; Zatorre et al., 2007). Estas funciones se comparten en gran medida entre los dos dominios (música y lenguaje) y, anatómicamente, están representadas principalmente en regiones superiores y mediales del lóbulo temporal, en zonas inferiores y medias del lóbulo frontal, en zonas del parietal inferior y en estructuras subcorticales, tales como los ganglios basales, el hipocampo y el cerebelo, así como en los haces de sustancia blanca que conectan todas estas regiones (Hoch, Poulin-Charronnat y Tillmann, 2011; Jentschke, Koelsch, Sallat y Friederici, 2008; Koelsch, Gunter, Wittfoth y Sammler, 2005; Patel, 2003; Patel, Iversen, Wassenaar y Hagoort, 2008; Tillmann, 2012).

Mediante el uso de métodos de resonancia magnética estructural y de tareas conductuales, esta tesis pretende ampliar nuestros conocimientos sobre las predisposiciones y la variabilidad individual en las habilidades para el lenguaje y la música, así como sus correlatos neuro-anatómicos. Además, también pretende ampliar nuestro conocimiento actual con respecto a los procesos de plasticidad cerebral y los cambios estructurales que se relacionan con la exposición a la música y con la práctica musical mantenida. Esta tesis contiene tres experimentos que, aunque independientes entre sí, comparten un enfoque común sobre la anatomía del cerebro relacionada con el procesamiento y el aprendizaje de funciones auditivo-motoras.

La presente tesis se presenta como compendio de publicaciones, teniendo un estudio publicado en la revista *NeuroImage* y otro en la revista *Cerebral Cortex*. Los datos expuestos en esta tesis son totalmente nuevos y no han sido ni van a ser incluidos en ninguna otra tesis.

En el **Estudio I** nuestro objetivo era comparar las características neuroanatómicas y posibles diferencias en la estructura cerebral entre un grupo de músicos profesionales de alto nivel (todos ellos pianistas) y un grupo de controles sin formación musical. Además, dentro del grupo de músicos, nos interesaba también investigar las posibles diferencias entre aquellos pianistas que empezaron a tocar a una edad temprana (edad de inicio < 7 años) y aquellos que comenzaron su entrenamiento musical más tarde (edad de inicio ≥ 7 años). Se controló por la edad de los participantes en el momento de su inclusión en el estudio, así como por la cantidad de horas de práctica desde el comienzo del entrenamiento musical y hasta el momento del estudio (en el caso de los pianistas).

Para ello, datos de neuroimagen estructural (secuencia T1) fueron recogidos para los dos grupos de participantes, analizándolos más tarde con la técnica de morfometría basada en el vóxel (VBM por sus siglas en inglés). Con el objetivo de obtener una medida de las habilidades pianísticas de los músicos incluidos en nuestra muestra, éstos completaron una tarea en la que debían tocar escalas con una u otra mano, alternativamente. En esta tarea se midió la precisión temporal durante la ejecución musical. Los resultados de este estudio muestran un patrón de hallazgos neuroestructurales más complejo que el descrito con anterioridad. En lugar de encontrar únicamente un aumento de sustancia gris en los músicos (Bermudez et al., 2009; Gaser & Schlaug, 2003; Luders et al., 2004; Schlaug et al., 1995; Schneider et al., 2002, 2005a, b), los pianistas en el presente trabajo mostraban un incremento en la sustancia gris en ciertas áreas (regiones relacionadas con el aprendizaje motor, la memoria, la automatización de movimientos o el procesamiento auditivo con componente emocional: hipocampo, amígdala, ganglios basales, regiones temporales superiores, entre otras), mientras que otras zonas evidenciaban una reducción de la sustancia gris (zonas temporales superiores, y áreas sensoriomotora y de integración sensorial en el hemisferio derecho), al ser comparados con los no-músicos.

Además, cuando comparamos a los músicos que empezaron a tocar el piano a edad temprana con aquellos que empezaron su entrenamiento después de los 7 años de edad, comprobamos que los pianistas que empezaron a practicar piano más jóvenes mostraban menos variabilidad temporal en la tarea de tocar escalas en el piano, así como menos sustancia gris (SG) en el putamen derecho. Este resultado se interpretó como que los pianistas de formación temprana pueden haber tenido un mayor refinamiento tanto de las vías neurales utilizadas durante la práctica musical, como de su técnica pianística, por el hecho de haber empezado la práctica musical en una época en la que el cerebro es especialmente plástico y está más predispuesto al aprendizaje y a la retención de nueva información (en comparación con otra épocas de la vida). Esta interpretación se apoya en el hecho de que los dos grupos de pianistas estaban emparejados por edad en el momento del estudio y horas de práctica actuales y pasadas y, por tanto, sólo diferían en la edad de inicio del aprendizaje musical. Estos resultados apoyan investigaciones previas que muestran este tipo de reducción en la SG del putamen en aquellos músicos que empezaron a practicar a edad temprana y que muestran grandes habilidades pianísticas (Granert et al., 2011; James et al., 2014).

En el **Estudio II** participaron individuos sanos cuya lengua materna era el alemán y que no habían tenido contacto previo con las lenguas derivadas del Hindustani. Se recogieron datos de neuroimagen estructural (imágenes de difusión para estudiar la sustancia blanca). Además, los participantes completaron una tarea conductual en la que escuchaban frases y una palabra en Hindi (condición de escucha para cada estímulo: 3 repeticiones) y, tras la última repetición, debían tratar de imitar la frase o palabra que hubieran escuchado, sin poder practicarla ni volver a escucharla. Para cada participante, la imitación directa de cada estímulo fue grabada; estas grabaciones fueron enviadas a 30 nativos de Hindi, que valoraron las grabaciones basándose en “cómo de nativo sonaban”. Por otra parte, los datos de difusión se diseccionaron usando dos técnicas de tractografía: (i) una determinística manual, que se ajusta a las particularidades de la anatomía de cada participante; y (ii) un método automático que combina una aproximación determinística con una disección basada en atlas y correcciones hechas a bases de modelos probabilísticos. Concretamente, las dos técnicas fueron empleadas para diseccionar el fascículo arqueado, que conecta áreas frontales, parietales y temporales. El fascículo arqueado está dividido en tres segmentos: largo (conectando áreas frontales inferiores –área de Broca– con áreas temporales superiores –área de Wernicke–), anterior (que conecta áreas frontales inferiores con áreas parietales inferiores –zona de Geschwind–), y posterior (conectando la región temporal superior con la zona parietal inferior). La valoración numérica asignada por los nativos que valoraron las imitaciones fue correlacionada con medidas de organización microestructural (volumen y anisotropía fraccional) del fascículo arqueado.

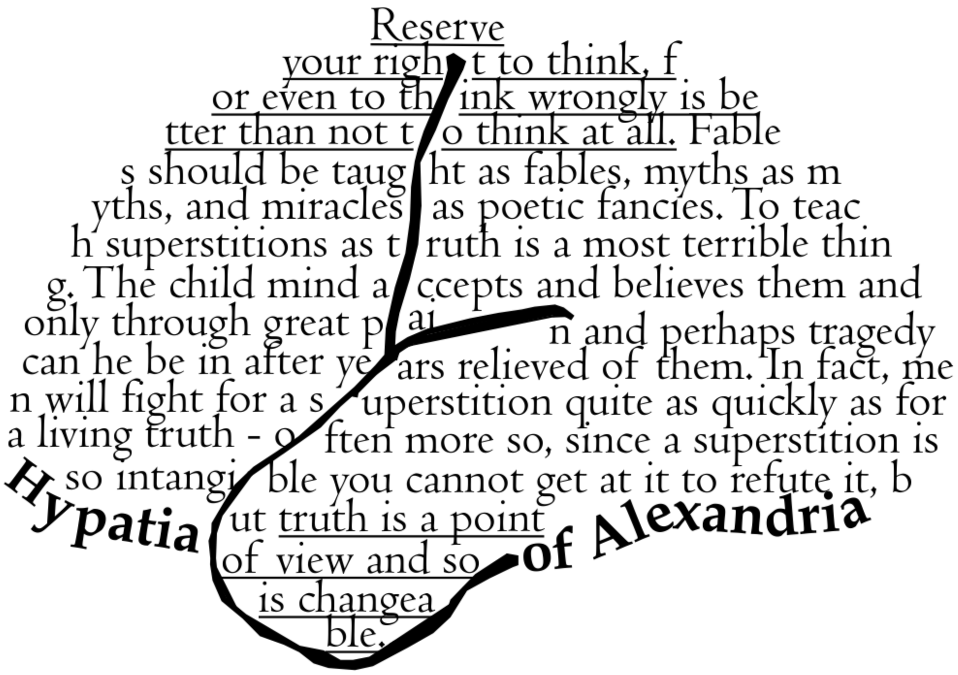
Los resultados de este estudio mostraron que el volumen del fascículo arqueado predice la calidad de la imitación de un lenguaje desconocido. Concretamente, encontramos que cuanto más lateralizado esté el fascículo arqueado hacia la izquierda en cuanto a su volumen, mejor es la imitación de Hindi (según los valores asignados por los nativos). Como conclusión, este estudio demostró que la organización microestructural de los haces de sustancia blanca puede predecir la variabilidad individual en la realización de tareas de imitación de lenguaje. Además, nuestros resultados apoyan lo encontrado en estudios anteriores: el fascículo arqueado es una vía con un papel crucial en las transformaciones audio-motoras necesarias durante el procesamiento y la producción del lenguaje. Nuestros resultados apuntan, por tanto, a que el fascículo arqueado es el sustrato principal de una red de retroalimentación y corrección que involucra las áreas frontales inferiores, temporales superiores y parietales inferiores, y que asegura una percepción correcta, una coordinada planificación motora, la monitorización de la producción en tiempo real y la corrección de los patrones motores cuando se detecten errores en la producción.

En el **Estudio III** decidimos estudiar si ciertos haces de sustancia blanca (SB) que habían sido reportados con anterioridad en estudios que comparaban músicos profesionales con no músicos podrían estar involucrados en los primeros estadios del aprendizaje musical, y si su microestructura podría predecir las diferencias individuales en el aprendizaje musical en no-músicos. Para ello, recogimos datos de neuroimagen estructural (imágenes de difusión) de 44 participantes castellano-catalano parlantes sin formación musical. En otra sesión, siempre después de la sesión de resonancia magnética, los participantes completaron un protocolo conductual de aprendizaje musical rápido (FML por sus siglas en inglés) en la que se les pedía realizar una tarea de sincronización rítmica (basada en Bailey & Penhune, 2012; Padrao et al., 2013) y otra de aprendizaje de melodías en el piano (inspirada en la usada por Chen et al., 2012). Sobre las imágenes estructurales de difusión se aplicó tractografia determinística para diseccionar manualmente el tracto cortico-espinal y el fascículo arqueado, bilateralmente. Por otra parte, de las tareas musicales se extrajeron diferentes medidas de aprendizaje (como la media de asincronía, el porcentaje de respuestas correctas o la velocidad de aprendizaje), que se correlacionaron con las medidas de organización microestructural (volumen y anisotropía fraccional) de los tractos diseccionados.

Los resultados nos muestran una clara lateralización a la derecha: (i) el volumen del tracto cortico-espinal derecho predijo la ejecución inicial en la tarea de sincronización rítmica, y (ii) el volumen del fascículo arqueado derecho predijo la tasa de aprendizaje en la sincronización durante la tarea de ritmos, y el volumen y la anisotropía fraccional del arqueado derecho predijeron la velocidad de aprendizaje en la tarea de melodías. Además, mirando los efectos en los diferentes segmentos del fascículos arqueado por separado, encontramos que la anisotropía fraccional en el segmento largo (directo) del hemisferio derecho correlacionaba con la velocidad de aprendizaje en la tarea de melodías, el volumen del segmento anterior del hemisferio derecho predijo la mejora en la sincronización (tasa de aprendizaje), y la anisotropía fraccional en el segmento posterior del hemisferio derecho estaba relacionada con la capacidad de adaptar los patrones rítmicos internos con el modelo externo (desviación del intervalo de la secuencia de respuestas dadas por el participante en comparación con el modelo).

Como **conclusión**, en la presente tesis, en primer lugar, se quisieron estudiar los cambios plásticos a nivel neuroanatómico provocados por la práctica musical a largo plazo (Estudio I). Sin embargo, después de este primer experimento, tenía curiosidad sobre el estado inicial del cerebro, antes de que cualquier entrenamiento se haya llevado a cabo. Para ello, se recogieron datos de individuos sanos sin formación musical (no músicos) y se midieron (conductualmente) sus habilidades para imitar un idioma extranjero novedoso (Estudio II); por último, obtuvimos datos de otra cohorte de individuos sin antecedentes musicales en los que investigamos habilidades musicales y su relación con la sustancia blanca cerebral. El hallazgo más interesante encontrado a través de los tres estudios, es la involucración del fascículo arqueado y las áreas corticales que éste conecta en actividades auditivo-motoras. A la luz de nuestros resultados, sugerimos que el fascículo arqueado desempeña un papel crucial en la transformación audio-motora que se requiere en actividades musicales y lingüísticas, sirviendo de eje para el circuito de retroalimentación (*feedback*) y alimentación directa (*feedforward*), gracias al cual se crean predicciones y se monitoriza la producción para comprobar que concuerde con los modelos almacenados en el sistema. Además, el presente trabajo apoya estudios previos que han usado el análisis correlacional para estudiar diferencias interindividuales, demostrando que ciertos marcadores microestructurales (de SG y SB) correlacionan y son capaces de predecir la ejecución en tareas musicales y lingüísticas. Pese a que los datos actuales nos impiden la realización de conclusiones categóricas respecto a la contribución genética vs. ambiental en las actividades lingüísticas y motoras, tanto el fondo genético como las experiencias a lo largo de nuestra vida tienen una influencia en nuestro comportamiento, cambiando también nuestra estructura cerebral. Sin embargo, son necesarios más estudios en este campo (i) para ampliar nuestro conocimiento sobre el procesamiento compartido entre lenguaje y música; (ii) para tratar de disociar las influencias genéticas de las ambientales (mediadas por procesos de neuroplasticidad) en el procesamiento de estos dos dominios; (iii) así como para categorizar los beneficios que el entrenamiento en una de estas actividades puede tener y cómo pueden transferirse estos beneficios a otros aspectos cognitivos. La importancia de los estudios en la línea seguida en la presente tesis se explica por la posible aplicación de sus resultados en aspectos sociales de gran relevancia. Concretamente, los entrenamientos musicales podrían aplicarse tanto en educación como en rehabilitación motora y del lenguaje; además, descubrir más detalles sobre el procesamiento de la música y del lenguaje podría ser útil en la realización de entrenamientos más personalizados, adaptados a las capacidades y habilidades de cada individuo, tendrían como resultado un aprendizaje más eficiente.

Chapter 9 - References



Reserve your right to think, for even to think wrongly is better than not to think at all. Fables should be taught as fables, myths as myths, and miracles as poetic fancies. To teach superstitions as truth is a most terrible thing. The child mind accepts and believes them and only through great pain and perhaps tragedy can he be in after years relieved of them. In fact, men will fight for a superstition quite as quickly as for a living truth - often more so, since a superstition is so intangible you cannot get at it to refute it, but truth is a point of view and so is changeable.

Hypatia of Alexandria

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Quotes included in the chapter's covers

Introduction

> *"Imagination is more important than knowledge."*
>
> *"Any man who reads too much and uses his own brain too little falls into lazy habits of thinking."*

By Albert Einstein (as cited by Forman, L. E. (2010). '*Albert Einstein: Physicist and Genius.'*).

Research aims

> *"When it is obvious that the goals cannot be reached, don't adjust the goals, adjust the action steps."*

By Confucius.

Study I

> *"Everybody knows that the ability of a pianist [. . . to play an] adaptation to the new work [. . .] requires many years of mental and muscular gymnastics. To understand this important phenomenon, it is necessary to accept that, in addition to the reinforcement of pre-established organic pathways, new pathways are created by the ramification and progressive growth of terminal dendritic and axonal processes."*

By Ramón y Cajal **(**'*Texture of the nervous system of man and the vertebrates*'**)**

Study II

> *"I was delighted when I first discovered that a pleasant sound, which often saluted my ears, proceeded from the throats of the little winged animals who had often intercepted the light from my eyes. (...) Sometimes I tried to imitate the pleasant*

> *songs of the birds, but was unable. Sometimes I wished to express my sensations in my own mode, but the uncouth and inarticulate sounds which broke from me frightened me into silence again."*

By Mary Shelley ('*Frankestein*')

Study III

> *"Life is fair. We all get the same nine-month shake in the box, and then the dice roll. Some people get a run of sevens. Some people, unfortunately, get snake-eyes. Its just how the world is."*

By Stephen King ('*Full Dark, No Stars*').

> *"Talent is a dull knife that will cut nothing unless it is wielded with great force"*

By Stephen King ('*Doctor Sleep*').

General discussion

> *"The snake which cannot cast its skin has to die. As well the minds which are prevented from changing their opinions; they cease to be mind."*
>
> *"You have your way. I have my way. As for the right way, the correct way, and the only way, it does not exist."*
>
> *"Without music, life would be a mistake."*
>
> *"There are no facts, only interpretations."*
>
> *"We should consider every day lost on which we have not danced at least once."*

By Frierdrich Nietzsche ('*Thus Spoke Zarathustra*', '*Twilight of the Idols*')

Conclusion

> *'I had worked hard for nearly two years, for the sole purpose of infusing life into an inanimate body. For this I had deprived myself of rest and health. I had desired it with an ardour that far exceed moderation; but now that I had finished, the beauty of the dream vanished, and breathless horror and disgust filled my heart. Unable to endure the aspect of the being I had created, I rushed out of the room and…*

By Mary Shelley ('*Frankestein*')

Resumen en castellano

> *"El arte es la ciencia de lo inútil. (…) El hombre es el único animal que se crea necesidades que nada tienen que ver con la subsistencia del individuo y con la reproducción de la especie. No le basta comer para alimentarse, sino que condimenta los alimentos, de modo que añadan placer a la satisfacción de su necesidad. No la basta vestirse para abrigarse, sino que añade, a esta función tan elemental, la exigencia de confeccionar su ropa con determinadas formas y colores. No se contenta con cobijarse, sino que construye edificios con líneas armoniosas y caprichosas que exceden de su necesidad: lo cual no ocurre con la guarida del zorro, la madriguera del conejo o el nido de la cigüeña. ¿Hay algo más inútil que la corbata que lleva usted puesta? ¿De qué le sirve al estómago una salsa Cumberland o un chateaubriand a la Périgord? (…) todo eso que está inútilmente "añadido a la pura necesidad"…¡ya es arte! (…) En el momento mismo en que el espíritu creador del hombre se despegó incluso de la necesidad primaria para producir sus lucubraciones, nacieron las grandes Artes: la Poesía, la Danza, la Música y la Pintura. (…) La danza (…) se aleja más de la necesidad (…) es una mímica sublimada. Tal vez la danza sea anterior al lenguaje y tuviera en sus orígenes una intencionalidad práctica: con carga erótica, reverencial o religiosa. (…) no hay duda que encerraba un propósito, encaminado a la consecuencia de un fin. (…) la intencionalidad es alogmuy superior a la "necesidad primaria". (…) Queda por último, la Música. ¿Qué mayor inutilidad que unir unos ruidos con otros*

> *ruidos que no expresan directamente nada y que pueden ser interpretados de mil distintas maneras según el estado de ánimo de quien los escuche? ¿A quién alimenta eso? ¿A quién abriga? ¿A quién cobija? ¡A nadie! La Música es la más inútil, biológicamente hablando, de todas las artes y, por ello, por su pavorosa y radical inutilidad, es la más grande de todas ellas; la menos irracional, la más intelectual, la más espiritual, la más humana, en tanto que esto signifique superación de los seres inferiores."*

By Torcuato Luca de Tena ('*Los renglones torcidos de dios*')

References

> *"Reserve your right to think, for even to think wrongly is better than not to think at all."*
>
> *"Fables should be taught as fables, myths as myths, and miracles as poetic fancies. To teach superstitions as truth is a most terrible thing. The child mind accepts and believes them and only through great pain and perhaps tragedy can he be in after years relieved of them. In fact, men will fight for a superstition quite as quickly as for a living truth – often more so, since a superstition is so intangible you cannot get at it to refute it, but truth is a point of view, and so is changeable."*

By Hypatia of Alexandria