



PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE
Doctorado en Neurociencias

Doctoral Thesis

**Functional and structural neural correlates of attention
and memory during bimodal (auditory/visual) stimuli in
children who play a musical instrument**

By

Leonie Margarita Kausel Kamp

October 2018



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children who play a musical instrument**

Thesis presented to the Pontificia Universidad Católica de Chile to qualify for the degree of
PhD in Neuroscience

By

Leonie Margarita Kausel Kamp

Thesis Director: Francisco Aboitiz
Thesis Co-director: Francisco Zamorano

Thesis committee: Sergio Ruiz
Eugenio Rodríguez
Gottfried Schlaug

October 19th, 2018



PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE
Doctorado en Neurociencias

El Comité de Tesis, constituido por los Profesores abajo firmantes, aprueba la Defensa
Publica de la Tesis Doctoral titulada:

**FUNCTIONAL AND STRUCTURAL NEURAL CORRELATES OF ATTENTION
AND MEMORY DURING BIMODAL (AUDITORY/VISUAL) STIMULI IN
CHILDREN WHO PLAY A MUSICAL INSTRUMENT**

Aprobación Defensa:

LEONIE MARGARITA KAUSEL KAMP

Calificándose el trabajo realizado, el manuscrito sometido y la defensa oral, con nota

..... (.....)

Dr. Mauricio Cuello
Director de Investigación y Doctorado
Escuela de Medicina
Pontificia Universidad Católica de Chile

Dr. Felipe Heusser
Decano
Facultad de Medicina
Pontificia Universidad Católica de Chile

Dra. Claudia Sáez
Sub-Directora
Dirección de Investigación y Doctorado
Escuela de Medicina
Pontificia Universidad Católica de Chile

Dr. Francisco Aboitiz
Director de Tesis
Escuela de Medicina
Pontificia Universidad Católica de Chile

Dr. Francisco Zamorano
Co-Director de Tesis
Facultad de Gobierno
Universidad de Desarrollo

Prof. Sergio Ruiz
Profesor Evaluador Interno
Escuela de Medicina
Pontificia Universidad Católica de Chile

Prof. Eugenio Rodríguez
Profesor Evaluador Interno
Escuela de Psicología
Pontificia Universidad Católica de Chile

Prof. Gottfried Schlaug
Profesor Evaluador Externo
Neurology Department
Beth Israel Deaconess Medical Center/Harvard Medical School

Santiago, 19 de octubre de 2018

Dedicated to

*My former violin students who inspired me to propose this research and to all
the children who take pleasure in the joy of playing a musical instrument*

Acknowledgments

I would like to thank all the people that from near and far have been with me in this adventure. If I had to describe my experience during my PhD it would be as a happy and intense time. I had the opportunity to meet wonderful people and make true friends. I also got married to the love of my life and I got the beautiful and important mission to be Sofia's godmother. And over all, I had the opportunity to make research in cognitive neuroscience, a fascinating topic by itself and more considering that I could investigate a subject which I am passionate about. I also got to know myself better. Like when after initially being worried about the fact that I did not experience the McGurk effect, I found a paper that showed that musicians do not perceive this illusion.

First, I would like to thank my family. My parents and my brother for always supporting and inspiring me along my life. And of course, my husband, who has been a fundamental support and a source of joy and peace since we are together. Special thanks also to my mom for critically reading and commenting on my multiple thesis versions and to Seba for always correcting my English and for reminding me to maintain scientific rigor at every point. Second, I would like to thank both my advisors. To Dr. Francisco Aboitiz, who always encouraged and supported me and gave me total liberty to develop my research. And to Dr. Francisco Zamorano, Pancho, who was my day to day advisor and taught me everything I know about MRI analysis and who invited me to carry out the research at our wonderful scanner in the Clínica Alemana. Without their fundamental support I could not have carried out this thesis. Also, I would like to thank all the support I got at the NeuroCICS at the UDD, where Pancho is a professor. Dr. Pablo Billeke was always there to help and teach me about EEG and any other kind of analysis, and Josefina helped me to recruit and evaluated nearly all the controls that are part of this thesis. Alejandra has also been an important support in the last months, standing by with advice and organizing outings to have a good time together.

I made important friends during my time in the PhD. I am glad that our ways crossed and that we got to know each other. Felipe, whom I met while signing up and the university and is since then a close friend. Dani, whom we adopted into our generation. All my generation classmates, Cristian, Jaime, Rafa, Ariel, Germán and Trini. Of course, Isma and Flo, who have become indispensable partners in all our crazy ventures, like the NeuroFeria and the Jornada para Jóvenes Científicos. Gonza, with whom we shared the exciting U21 research. And all my other PhD classmates, like David,

Paty, Marcos, Seba, Ernesto and all others who made this PhD such an enriching experience. Also, to my old friends from school, university, orchestra and life. Specially to Pauli, who is also in her PhD, so we did understand and comfort each other when the work seemed to get over us.

I would also like to thank Dr. Gottfried Schlaug for accepting me in his lab for the internship. This gave me the opportunity to spend a time in one of the pioneering labs in neuroscience and music, and also allowed me to enjoy one of the most intellectually vibrant cities for a few months. He and his team, Anant, Fanny, Sebastien, Andrea and Karen made my stay in Boston a huge pleasure and a very productive time.

Additionally, I would like to thank Claudia Andrade for all the support that she gave me and gives us in the program. It is really always a joy and a relieve to know that she is there. I would also like to thank Mary Elizabeth for being there at the beginning and helping me to line out my research and creating all the auditory stimuli of our task, Maestro César and his team for helping me with the scanner, Jani Brouwer for always feeling her support in the university, Paty for helping me with the EEGs, Isabel for helping and making some EEGs while I was not here, Debbie for sending me all the certificates I needed for Conicyt, Pablo Fuentealba for supporting us in our doctorate program, the orchestra conductors who welcomed me to invite the musically trained children, Sebas' family for all their support and all the other people who were there and helped me on this path. Furthermore, I would also like to thank my thesis committee for accepting the challenge of handing in this thesis and for all the helpful comments and suggestions that they gave me while carrying out my research.

Finally, I would like to give a very big thank you to all my participants and their parents for their commitment, which made this research possible.

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Abbreviations

AC	attention condition
ACC	anterior cingulate cortex
AMT	auditory memory task
ASA	auditory selective attention condition
DA	divided attention condition
dIPFC	dorsolateral prefrontal cortex
DTI	diffusion tensor imaging
(f)MRI	(functional) magnetic resonance imaging
IFG	inferior frontal gyrus
P	passive condition
SMA	supplementary motor area
SMG	supramarginal gyrus
TBSS	tract-based spatial statistics
VBM	voxel-based morphometry
VMT	visual memory task
VSA	visual selective attention condition
WM	working memory

1 Abstract

The ability to focus on one or more stimuli at the same time is a crucial capacity that allows us to cope successfully with our daily life. Since playing a musical instrument demands to pay attention to lots of events at the same time, we hypothesized that this activity trains these types of attention, and that the neural networks underlying these skills would be boosted in children who regularly learn and play a musical instrument. To test our hypothesis, we asked children aged 10 to 13 with and without musical training to complete a selective and divided attention task while their brain activity was measured with fMRI. The task presented a pair of bimodal stimuli (melody and figure) to the participants and they were asked to pay attention only to the auditory, only to the visual, or to both stimuli at the same time. Both stimuli were tested with a same/different memory task after presentation in order to confirm attention allocation. Our study showed that both groups were able to follow the attention instructions, showing a better performance on the memory tasks of the items that they were instructed to attend, but musically trained children had an overall better performance on both memory tasks. This difference between groups in overall performance was guided by higher activation in musicians of the fronto-parietal attention network and the thalamus among others in the encoding phase of in the three attention conditions. In addition, we found that the better performance of musically trained children on the auditory memory tasks was not only due to improved allocation of attentional resources, but also due to facilitated encoding of auditory stimuli given by the years of training that depended on the left inferior frontal gyrus (IFG) and left supramarginal gyrus (SMG), which are part of the phonological loop. Therefore, our results strongly suggest that two distinct neural mechanisms played a role in the better performance of musically trained children on our task. Based on our results, we propose a mechanistic framework that allows to interpret the observations that have been made on the impact of musical training across lifespan. Our results could be relevant for educational and public health policies, and they also suggest that musical training could be used as a non-pharmacological intervention strategy for children with attentional problems.

2 Introduction

Our experience in daily life, what we see, hear, remember and learn, depends not only on the information entering our senses, but also upon which aspects we choose to attend (Aboitiz & Cosmelli, 2009; Driver, 2001). Our brain controls what we attend and remember, which in turn is fundamental for achieving efficient cognitive functioning (Frith, 2011; Posner & Rothbart, 2014).

Goal-directed attention and working-memory capacity are key components of executive functions, which are highly relevant for academic foundations and are also involved in the regulation of thoughts, emotions and decision-making (Rueda et al., 2012). These skills last a lifetime and are used every day to interact with our world. When children have opportunities to develop executive function skills, individuals and society experience lifelong benefits (Developing Child, 2018; Hinton et al., 2012).

One activity that has shown evidence of enhancing executive functions is musical training (Bialystok & DePape, 2009; Moreno et al., 2011; Slevc et al., 2016). Playing a musical instrument requires musicians to continuously switch between reading notes and translating them into meaningful sounds by monitoring and adjusting fine finger movements. Furthermore, when playing in a group, musicians have to attend to new and competing streams of auditory information from other performers as well as their own playing (Rodrigues et al., 2013). It is likely that mastering such skills can lead to improvements in nonmusical cognitive domains. Indeed, several studies have shown that individuals with music training outperform their musically untrained peers in tasks assessing executive functions, including auditory working memory. Duration of musical training has also been associated with better performance on auditory and visual forms of the Stroop tasks, even when the visual results have not been consistent (Habibi et al., 2018; Talamini et al., 2017). Nevertheless, the neural correlates that underlie these improvements in executive functioning in musicians are very little explored.

We decided to gain insight into this topic by investigating the neural correlates of bimodal (auditory/visual) attention and working memory in musically trained children as compared to control children. Since we live in a multimodal world, we were particularly interested in exploring the effect of musical training with a more naturalistic paradigm. We hypothesized that playing a

musical instrument trains selective and divided attention for the auditory modality in children, and that the neural networks underlying these attention skills would be boosted in children who regularly learn and play a musical instrument.

To test our hypothesis, we designed and completed a cross-sectional study in which 41 children aged 10 to 13 (20 musically trained children (3.7 ± 1.3 years of training); 21 control children) solved a bimodal (auditory/visual) attention task adapted from Johnson & Zatorre (2006) while their brain activity was measured with functional magnetic resonance imaging. Groups were matched for gender, age, intelligence coefficient and socioeconomic status. Each trial of our task had two parts, the encoding phase and the memory tasks. The encoding phase started with an attention instruction and then presented a pair of stimuli, which included a figure (visual) and a melody (auditory). The initial attention instruction asked children to pay attention either to the auditory, to the visual or to both stimuli at the same time. This defined the auditory selective, the visual selective and the divided attention condition, respectively. We also included one instruction that asked the children to passively observe the stimuli. This was the passive condition and these trials did not include the memory tasks. Same/different memory tasks for both the auditory and the visual stimulus followed each active attention encoding phase in order to evaluate attention. A better performance on the memory task for the attended stimuli was expected.

Our study showed that musically trained children had an overall better performance in auditory and visual memory tasks, and that this was guided by higher activation of the fronto-parietal attention network and subcortical cognitive control areas such as the thalamus in musically trained children as compared to control children. Our findings also suggested that the better performance of musically trained children in our attention task was not only due to improved allocation of attentional resources, but also due to facilitated encoding of auditory stimuli given by years of training that depends on the left inferior frontal gyrus (IFG) and left supramarginal gyrus (SMG). Based on our results, we were able to propose a framework that suggests that two distinct neural mechanisms underlie the impact of musical training on executive functioning across lifespan.

In conclusion, our study showed enhanced executive function skills in musically trained children as compared to control children. Our research allowed us to gain a new insight into the neurobiology of attentional control and memory mechanisms that seem to be enhanced in musically trained

children and most importantly, they allowed us to propose a framework including two distinct neural mechanisms that underlie the effect of musical training on executive functions. Our results and proposed framework give a whole new insight into the effects of musical training on executive functions across lifespan and could be relevant for educational and public health policies. They also suggest that musical training could be used as a non-pharmacological intervention strategy for children with attentional problems.

3 Background

3.1 Attention and working memory

Attention and memory are important cognitive functions that allow us to process and retain perceived sensory information from the environment. Attention allows us to select the stimuli that are relevant for us at each moment and working memory (WM) allows us to keep the information in an accessible state for a short time. These functions are closely related, mainly because paying attention to certain information makes it easier to remember (Fougnie, 2008).

Goal-directed attention and working-memory capacity are key components of executive functions, which are highly relevant for academic foundations and are also involved in the regulation of thoughts, emotions and decision-making (Rueda et al., 2012). These skills last a lifetime and are used every day to interact with our world. When children have opportunities to develop executive function skills, individuals and society experience lifelong benefits (Developing Child, 2018; Hinton et al., 2012).

3.1.1 Attention

As stated by the American philosopher and psychologist William James (1890):

“Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others, and is a condition, which has a real opposite in the confused, dazed, scatterbrained state, which in French is called distraction, and Zerstreutheit in German.”

Attention enables behavior by modulating both sensory inputs and task goals. Combining attentional resources from both of those sources allows us to cope successfully with every day demands (Carlson, 2013). Attended sensory information is processed more rapidly and accurately and with higher spatial resolution and sensitivity for fine changes, while non-attended information

appears lower in contrast and is sometimes not perceived at all (Aboitiz & Cosmelli, 2009; Wu, 2014). Also, human observers are better at detecting an object in a visual scene when they know in advance something about its features, such as its location, motion or color. This facilitation depends on our ability to represent this advance information (a “perceptual set”), and to use it to bias the processing of incoming visual information. Similarly, responses to a stimulus are quicker when subjects know in advance what type of movement they have to make (such as which arm to move or the direction of the movement — a “motor set”) (Maurizio Corbetta & Shulman, 2002).

Importantly, a functional attentional system is critical to ensure that we can navigate an unpredictable world while keeping in accordance with experience-dependent goals yet allowing for behavioral novelty through spontaneous exploration. An unbalance in any of these three processes will inevitably lead to departures from what we usually understand as “normal” or “healthy” behavior (Aboitiz & Cosmelli, 2009; Dajani & Uddin, 2015).

3.1.2 Selective and divided attention

Goal-directed attention can be described as being selective or divided. Selective attention is when attentional resources are focused on a single stimulus, ignoring all others, whereas divided attention is when attentional resources are distributed among two or more stimuli (M. Corbetta et al., 1991). One type of divided attention is multimodal divided attention, during which attentional resources are distributed among different sensory modalities, such as vision and audition (Yang et al., 2013). Divided attention tasks are more complex and generally require more processing operations, which often leads to a decrease in the speed and accuracy of performance (M. Corbetta et al., 1991; Pashler, 1994).

Changing between attentional states during selective and divided attention tasks also implies cognitive flexibility. Cognitive flexibility is the ability to appropriately adjust one’s behavior according to a changing environment. Cognitive flexibility enables an individual to work efficiently to disengage from a previous task, reconfigure a new response set, and implement this new response set to the task at hand. Greater cognitive flexibility is associated with favorable outcomes throughout the lifespan, such as better reading abilities in childhood, higher resilience to negative

life events and stress in adulthood, higher levels of creativity in adulthood, and better quality of life in older individuals (Dajani & Uddin, 2015).

3.1.3 Working memory

Memory is our ability to encode, store, retain and subsequently recall information and past experiences. The ability to keep representations in an active and accessible state gives us the capability to learn and adapt from previous experiences and is also very important for higher cognitive functions, such as planning, problem solving, and reasoning (Kandel et al., 2013). Attention and memory are strongly connected to each other. In order to remember information, one has to pay attention when that information is presented. This is why a very effective mode of evaluating attention is working memory. Working memory (WM) is short-term memory that has limited storage capacity and maintains current and transient representations of immediate goal-relevant knowledge (Baddeley, 1992, 2000).

According to Baddeley and Hitch's (1974) classic model and its several updates, WM consists of a central executive system that controls attentional resources and three subsidiary systems, the phonological loop, the visuospatial sketchpad and the episodic buffer. While the phonological loop stores and manipulates verbal information and also tonal stimuli, the visuospatial sketchpad stores and manipulates visual and spatial information. Finally, the episodic buffer holds representations that integrates phonological, visual, and spatial information, and is also the link between working memory and long-term memory. The component is episodic because it is assumed to bind information into a unitary episodic representation (Baddeley, 1992, 2000), .

It is widely accepted that working-memory capacity reflects the efficiency of executive functions (which include attention) and general intelligence, most notably the ability to maintain multiple task-relevant representations in the face of distracting irrelevant information; and that such tasks seem to reflect individual differences in the ability to focus and maintain attention, particularly when other events are serving to capture attention (Engle & Kane, 2004; Kane & Engle, 2002).

The storage capacity of working memory is limited but can be expanded by training, and evidence of the neural mechanisms underlying this effect is accumulating. Human imaging studies and neurophysiological recordings in non-human primates, together with computational modelling

studies, reveal that training increases the activity of prefrontal neurons and the strength of connectivity in the prefrontal cortex and between the prefrontal and parietal cortex. It has also been found that dopaminergic transmission seems to have a facilitatory role in this process (Constantinidis & Klingberg, 2016).

3.2 Neurobiology of attention and subsequent WM

The guiding of goal-directed attention is commonly agreed to be controlled by both bottom-up signals, with salient information guiding the allocation of attention, as well as in a top-down fashion whereby the goals of the participants also shape attentional allocation (Buschman & Kastner, 2015; Maurizio Corbetta & Shulman, 2002). Such stimulus-driven and goal-directed ways of controlling attention rely on partially overlapping networks of brain areas, and, while guided by separable operating principles, interact almost constantly to ultimately determine attention allocation (Stevens & Bavelier, 2012).

Both working memory and attention rely strongly, though not exclusively, on frontal brain areas (Kane & Engle, 2002; Riley & Constantinidis, 2016). A meta-analysis of structural neuroimaging studies showed that a larger prefrontal cortex (PFC) volume and greater PFC thickness were associated with better executive performances (Yuan & Raz, 2014). Lesion studies have also confirmed this fact, showing that lesions in PFC can result in important deficits of attention and WM (Godefroy & Rousseaux, 1996; Szczepanski & Knight, 2014).

It has been shown that goal-directed executive attention and working memory rely on the activation of a fronto-parietal control network, that includes the dorsolateral prefrontal cortex (dlPFC) and the superior parietal lobe (sPL) (Corbetta & Shulman, 2002). In particular, it has been suggested that the role of dlPFC is to maintain information in a highly active, easily accessible state (Kane & Engle, 2002). For instance, monkeys with lesions constrained to the dlPFC (BA9, 46 only) and humans with focal lesions to the analogous region have difficulty performing self-ordered working memory tasks, during which they are presented with arrangements of stimuli and must choose a different stimulus for every trial until all of the stimuli have been chosen once (Szczepanski & Knight, 2014). Tremblay et al. (2015) showed that the simultaneous activity of neuronal ensembles in the primate lateral PFC can be reliably decoded to predict the allocation of attention on a single-trial basis. Decoding was

sensitive to the noise correlation structure of the ensembles. Additionally, it was resilient to distractors, predictive of behavior, and stable over weeks.

The fronto-parietal control network seems to generate neural contrast by enhancing activity in sensory regions for items that are relevant and suppressing activity for items irrelevant to task goals. For example, in visual areas, excitability changes are reflected in competition for representations in receptive fields of individual neurons, baseline firing rates of neurons and synchronization of neuronal ensembles. It is now widely accepted that top-down modulation of sensory processing is not an intrinsic property of sensory cortices, but rather relies on long-range inputs from and interactions with a network of “control” regions, including the prefrontal and parietal cortex (Maurizio Corbetta & Shulman, 2002). The fronto-parietal control network is also activated when subjects select non-spatial information. In studies of feature-based attention, similar activations have been found when subjects shift attention from one feature to another (e.g., from color to direction of motion in a display of colored, moving dots) (Greenberg et al., 2010) or when subjects shift attention between two spatially overlapping objects and perform object-based selections (Serences et al., 2004). Together, these studies suggest that the fronto-parietal network is a “domain-general” controller (Buschman & Kastner, 2015). Functional connectivity measured in resting state, without specific task demands, also exhibit patterns of connectivity that closely resemble the frontoparietal attention network. Both task-related and resting-state networks exhibit consistent relations to behavioral measures of attention. Connectivity analyses applied to investigate cognitive differences across individuals in both healthy and diseased states suggest that disconnection of attentional networks is linked to deficits in cognitive functioning, and in extreme cases, to disorders of attention (Parks & Madden, 2013).

The most important neurotransmitter related to the to the execution of goal-directed behavior is dopamine. Dopaminergic innervation of the PFC originates from neurons within the ventral midbrain, including those within the ventral tegmental area (VTA). Compared with other subtypes, D1 receptors (D1R) are more abundant in the PFC and are believed to play a more prominent role in regulating cognitive functions (Squire et al., 2013). There are two main types of dopaminergic neurotransmission. Phasic transmission consists of strong but short-lasting trains of stimulus-related dopamine release; this has been considered to be mediated mainly by D1-like dopaminergic receptors in the case of dopamine. On the other hand, tonic liberation refers to the maintenance of

basal levels of extrasynaptic neurotransmitter and is mediated by D2-like receptors. Phasic activity is mediated by salient or motivating stimuli, while tonic activity defines a basal level of dopaminergic activity. An appropriate, alternating balance between phasic and tonic activity allows the initial focalization of behavior according to relevant stimuli (phasic transmission), while different levels of basal tonic activity may permit to maintain the focus over time as well as updating information in a changing context (Aboitiz et al., 2014).

Research also indicates that dopamine plays an important role in WM function. Early evidence for the involvement of D1R in WM processes comes from work by Müller et al. (1998) that showed that systemic injections of pergolide, a combined D1R/D2R agonist, but not bromocriptine, a D2R agonist, facilitated WM performance in a delayed matching task with delays of 2–16 s. These results implicated D1R and not D2R in WM modulation. The important role of D1R on WM is also suggested by the correlation between the decrease of D1R binding in the lateral PFC and the decrease in WM performance with age (Puig et al., 2014). Dopamine also seems to be involved in improving WM capacity. For example, pharmacological interventions acting on the dopaminergic system, such as methylphenidate, improve WM performance. In addition, behavioral interventions for improving WM performance in the form of intensive computerized training have recently been associated with changes in dopamine receptor density. These two different means of improving WM performance—pharmacological and behavioral—are thus associated with similar biological mechanisms in the brain involving dopaminergic systems (Söderqvist et al., 2012).

3.3 Development of attention and WM

Infancy is a period of great changes in brain structure and function that are reflected by the increase of processing capacities of the developing child. The emergence of complex cognitive functions, such as language, reasoning, and cognitive control, is a hallmark of human development (Nelson & Luciana, 2014). These abilities are made possible by a protracted trajectory of brain development and learning over the first two decades of life (Bressler & Menon, 2010). Understanding how the developing brain achieves such abilities ultimately depends on knowledge of how functional

interactions between distributed brain regions mature with age to produce sophisticated cognitive systems (Menon, 2013).

Brain anatomical changes during childhood and adolescence are increases in white matter volumes throughout the brain and regionally specific inverted U-shaped trajectories of gray matter volumes (Lenroot & Giedd, 2006). Behaviorally, while some aspects of attention are clearly present in some form in infancy, the ability to deploy and control directed attention continues to develop into early adulthood. For example, background noise creates greater interference effects for younger children and adolescents, who also show larger effects of flanker stimuli relative to adults (Ridderinkhof & van der Stelt, 2000). Findings suggest that the ability to control the deployment of attention is fragile in development, and while essentially available, attentional modulation may not be harnessed to the same degree by all children (Stevens & Bavelier, 2012).

Cognitive flexibility skills (which include attention and WM) begin to develop in early childhood, with a sharp increase in abilities between 7 and 9 years of age. Cognitive flexibility becomes largely mature by 10 years of age, but skills continue to improve throughout adolescence and into adulthood, reaching their peak between the ages of 21 and 30 years. Working memory also emerges early in toddlerhood and continues to improve throughout adolescence (Dajani & Uddin, 2015). There is evidence showing that the capacity of working memory is a strong predictor of cognitive abilities in childhood (Kail, 2007). Most studies of cognitive flexibility comparing children and adults find higher levels of, and more specific, activation in the frontal, parietal, and basal ganglia regions in adults and more dispersed activations in children, whereas others report little difference in brain activation between age groups (Dajani & Uddin, 2015).

Taken together, the brain is extremely plastic during development and when children have opportunities to develop and improve executive function skills, individuals and society experience lifelong benefits (Developing Child, 2018; Hinton et al., 2012).

3.4 Musical training

Playing a musical instrument is an intense, multisensory, and motor experience that usually commences at an early age and requires the acquisition and maintenance of a range of sensory and motor skills over the course of a musician's lifetime (Schlaug, 2015). Music making places unique demands on the nervous system and leads to a strong coupling of perception and action mediated by sensory, motor, and multimodal integrative regions distributed throughout the brain (Schlaug et al., 2010).

Playing an instrument requires a host of skills, including reading a complex symbolic system (musical notation) and translating it into sequential, bimanual motor activity dependent on multi-sensory feedback; developing fine motor skills coupled with metric precision; memorizing long musical passages; and improvising within given musical parameters (Wan & Schlaug, 2010).

The brain demonstrates a remarkable capacity to undergo structural and functional change in response to experience throughout the lifespan. Learning to play a musical instrument in childhood can result in long-lasting changes in brain organization (Wan & Schlaug, 2010). Studies have demonstrated functional and structural neuroplastic changes at cortical and subcortical regions associated with sensory, cognitive, and motor abilities in musicians (Münste et al., 2002; Pantev & Herholz, 2011; Wan & Schlaug, 2010; Zatorre et al., 2007). For example, differences between musicians and non-musicians reported larger anterior corpus callosum in musicians (Schlaug et al., 1995), a finding that has since been replicated by different research groups using different methodological approaches (e.g. Hyde et al., 2009). Musical training has also been shown to influence the plasticity of the superior longitudinal fasciculus, a tract that connects frontal and parietal regions of the brain among others, as a function of musical expertise (Oechslin, 2010). Longitudinally studies conducted on groups that were paired for general demographics before training (Habibi et al., 2017; Kraus et al., 2014; Putkinen et al., 2015; Schlaug et al., 2005), also suggest that musical training has a “nurture” effect on development and brain plasticity.

Research has also consistently shown that auditory attention and memory skills are (unsurprisingly) improved in musically trained people. Studies have shown that musicians have a superior performance in tasks involving the phonological loop; for example, musicians outperform non-

musicians in WM tasks that use music stimuli (Pallesen et al., 2010; K. Schulze, Dowling, & Tillmann, 2012; Schulze, Zysset, Mueller, Friederici, & Koelsch, 2011) and verbal material such as digits (Hansen et al., 2013; Lee et al., 2007; Ramachandra et al., 2012). In contrast, results in visual tasks (i.e., tasks that tap the visuospatial sketchpad) are mixed, with some studies showing better performance of musicians, and some not (Talamini et al., 2017). The neural correlates that underlie these improvements in executive functioning in musicians are currently a matter of intensive research. Recent studies have shown that musically trained children have higher activation of cognitive control related areas when solving a visual Stroop-task (Sachs et al., 2017), a sound working memory task (Pallesen et al., 2010) and a set-shifting task (Zuk et al., 2014). Driven by this research, musical training has been suggested to be a natural model of brain plasticity (Herholz & Zatorre, 2012; Münte et al., 2002; Schlaug, 2015) and has also been proposed as an alternative and effective method for neuro-education and neuro-rehabilitation (François et al., 2015).

Taken together, given the fact that musical training is a natural model to study neuroplasticity, we decided to add to this literature by investigating neural correlates of bimodal (auditory/visual) attention and working memory in musically trained children as compared to control children. Since we live in a multimodal world, we were particularly interested in exploring the effect of musical training on auditory and visual attention. We hypothesized that playing a musical instrument trains bimodal selective and divided attention in children, and that the neural networks underlying these attention skills would be boosted in children who regularly learn and play a musical instrument.

4 Hypotheses and objectives

4.1 Hypotheses

4.1.1 General hypothesis

Children who play musical instruments will show a higher activation of the fronto-parietal network and a better performance on the attention task as compared to controls. Structural correlates will be in line with attention enhancements.

4.1.2 Specific hypotheses

Musically trained children as compared to controls will show:

1. Better performance in the auditory memory task in the auditory selective attention and divided attention conditions
2. Higher activation of the fronto-parietal attention control network during the auditory selective attention and divided attention conditions
3. More gray matter in prefrontal regions (VBM) and more left than right asymmetry in the superior longitudinal fasciculus (DTI)

4.2 Objectives

4.2.1 General objective

To investigate functional and structural differences of the neural correlates of selective and divided attention and subsequent memory for simultaneous bimodal (auditory/visual) stimuli between children who play musical instruments and control children with functional magnetic resonance imaging.

4.2.2 Specific objectives

1. Explore whether accuracy (behavioral response) on the memory tasks in selective and divided attention conditions is increased in children who play a musical instrument compared to controls.
2. Characterize the functional neural correlates of attention and memory for musically trained and untrained children when they attend to one stimulus (ignoring the other) and when they attend to both stimuli simultaneously.
3. Determine if there are differences in functional neural correlates of selective and divided attention and subsequent memory between musically trained and non-trained children.
4. Determine if there are differences in structural neural correlates of attention and memory between musically trained and non-trained children that could relate to differences in the functional neural correlates of attention and memory and the performance in memory tasks.
5. Interpret the results of this thesis in the context of the existing literature.

5 Participants and Methods

5.1 Subjects

Forty-one healthy, right-handed, Spanish speaking children aged 10 to 13, with normal hearing and corrected-to-normal vision participated in our study after obtaining written informed consent from all children and their parents for a protocol approved by the ethics committee of the Pontificia Universidad Católica de Chile. Participants had to be willing to participate in three sessions: (1) psychological evaluation, (2) experimental magnetic resonance imaging (MRI) session and (3) experimental electroencephalography (EEG) session. The order of the last two sessions was counterbalanced across participants. In this thesis we present the MRI results. In the psychological evaluation participants completed the Wechsler Intellectual Scale for Children (WISC III) (Ramírez & Rosas, 2007; Wechsler, 1991) and in the EEG session they answered the Spanish version of the standardized Montreal Music History Questionnaire (Coffey et al., 2011), which inquiries about their personal experience in music listening and performing. Participants received monetary compensation for travel costs.

Musically trained children (Table I) were recruited from different youth orchestras of Santiago, Chile. Inclusion criteria included playing a melodic instrument, having at least of 2 years of instrumental lessons, practice at least 2 hours a week and regularly play in an orchestra or an ensemble. Six children played wind instruments (3 clarinets, 1 traverse flute, 1 horn, 1 saxophone) and 14 played string instruments (12 violins, 1 viola, 1 cello). Average musical training was 3.7 ± 1.3 years (range from 2 to 6 years) and all participants had studied music continuously since the onset of training. All children were trained based on more non-aural strategies and had individual or small group (2 – 3 participants) instrumental lessons and also played in an orchestra having rehearsals at least once a week. Control children were recruited from public schools in Santiago and had no additional musical training than the one provided in school curricula. In contrast to musically trained children, control children all declared to be unable to read or write musical scores.

Importantly, groups were matched for gender, age, intelligence coefficient (WISCIII) and socioeconomic status (educational level of both parents) (Table II). For parental education, the highest, successfully completed education level of the parents was re-coded into a measure

reflecting level of education, ranging from 1 (incomplete middle school education) to 10 (complete PhD). The average of both parents was used (Liberatos et al., 1988). The guardian of one musically trained child did not provide father education and the guardian of one control child did not provide parental education.

Musically trained children (n = 20)

<i>Group characteristics</i>	<i>Mean ± SD</i>	<i>Range</i>
Age at onset of musical training (years)	8.8 ± 1.9	4 - 11
Intensity of practice over the last year (hours/week)	9.4 ± 5.1	2 - 21
Duration of musical training (years)	3.7 ± 1.3	2 - 6
<i>Type of musical instrument</i>	<i>Number of children</i>	
Strings	14	
Woodwinds	4	
Brass	2	

Table I: Characteristics of musical training in musically trained children.

	Musically trained children	Control children	
n	20	21	
Females	11	12	
	Mean ± SD	Mean ± SD	t value (p value)
Age (years)	12.2 ± 0.8	12.0 ± 1.0	0.90 (0.19)
IQ	110.2 ± 9.9	105.7 ± 11.1	1.33 (0.10)
Parental education	4.0 ± 1.8	4.1 ± 1.5	-0.19 (0.58)

Table II: General demographics of the study population. There were no significant differences between groups for age, IQ and parental education. *IQ: intelligence coefficient.*

5.2 Experimental design

5.2.1 Experimental task

The bimodal (auditory/visual) attention task that was used in this thesis was adapted from Johnson & Zatorre (2006). Participants solved this task while their brain activity was measured with functional magnetic resonance imaging (fMRI).

5.2.2 Stimuli

Auditory (melodies) and visual (figures) stimuli were 4 seconds long, including a defined feature that would serve to direct attention to one modality during selective attention conditions.

Melodies were generated in Sibelius and were in major tonalities comprising pitches drawn from the Western musical scale centered around the mid-range of the piano from F3 (175 Hz) to G6 (784 Hz), with quarter and eighth notes. They were all in wav format and were presented in a piano timbre. All melodies contained one chord, which had to be reported by button press during the auditory selective attention condition. The melodies were presented binaurally at a comfortable listening level for each subject through MR-compatible sound transmission headphones (Resonance Technology Inc., <http://www.mrvideo.com/>).

Figures were created in Power Point and consisted of equally long nine black lines and one red line, which had to be reported by button press during visual selective attention condition. Individual shapes had the same starting point and lines were presented sequentially aligned either horizontally or vertically in order to “draw” a figure on a white background. Every 300ms a new line segment was presented and kept in view. After 3000ms a fully formed abstract shape remained in view for 1000ms. The MRI head coil had a mirror attached, so that participants could see the screen where visual stimuli were displayed. The screen was positioned at a comfortable viewing distance for each subject.

160 melodies and figures were created in total. When presented simultaneously, the auditory and visual stimuli started and stopped at exactly the same time but the individual elements of the two stimuli never synchronized. Stimuli were presented using Presentation Software (Neurobehavioral Systems).

5.2.3 Procedure

First the task presented an attention instruction followed by one stimuli pair that consisted of a melody (auditory) accompanied by an evolving abstract figure (visual). Attention conditions (AC) were given by instructions. Conditions included auditory selective attention (ASA) (“Pay attention only to the melody”), visual selective attention (VSA) (“Pay attention only to the figure”), divided attention (DA) (“Pay attention to both the figure and melody”) and passive (P) (“Passively observe both”). Each encoding phase (instructions + stimuli) consisted of instructions followed by 4s of simultaneously presented melody and figure. Ability to follow instructions was tested with a memory task (MT) for both melody (auditory memory task – AMT) and figure (visual memory task – VMT) that presented the actual stimulus or a foil stimulus. To answer the memory task subjects had to report via button press if they had previously heard or seen the stimulus. A better performance on the memory task of the attended stimuli was expected. Passive condition did not include the memory tasks. Each memory task consisted of a question (Do you remember?), followed by the presentation of either the same or a foil melody (AMT) or the same or a foil evolving abstract figure (VMT), finishing with the question to answer yes or no (Did you hear/see this melody/figure before?). Participants had 2.5 seconds to respond (Figure 1). Accuracy and reaction time on the memory tasks were our behavioral outcome measures.

For the three active attention conditions (ASA, VSA, DA), each trial consisted of the encoding phase (instructions + stimuli presentation) plus both memory tasks. Order of memory tasks was randomized for each trial. For the passive condition (P) trials consisted only of the encoding phase. The trials of each AC were presented as a block. Order of AC blocks was randomized across participants. All conditions included unique stimuli and stimuli pairs were defined randomly for each subject. One round had a duration of 16:05min and included 36 trials, 9 trials for each AC. Each participant completed 1 round of the task while being scanned in the MRI machine (Figure 2).

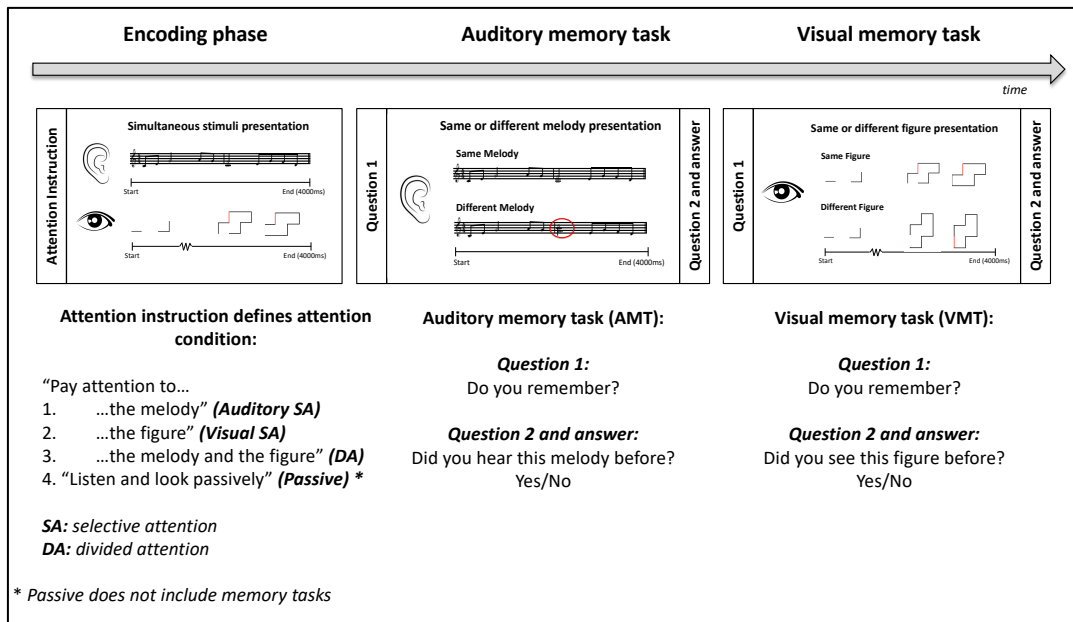


Figure 1: Bimodal (auditory/visual) attention task. Active attention conditions (ASA, VSA, DA) include encoding phase (instruction + stimuli presentation) and memory tasks. Order of memory tasks was randomized for each trial. Passive condition only includes encoding phase.

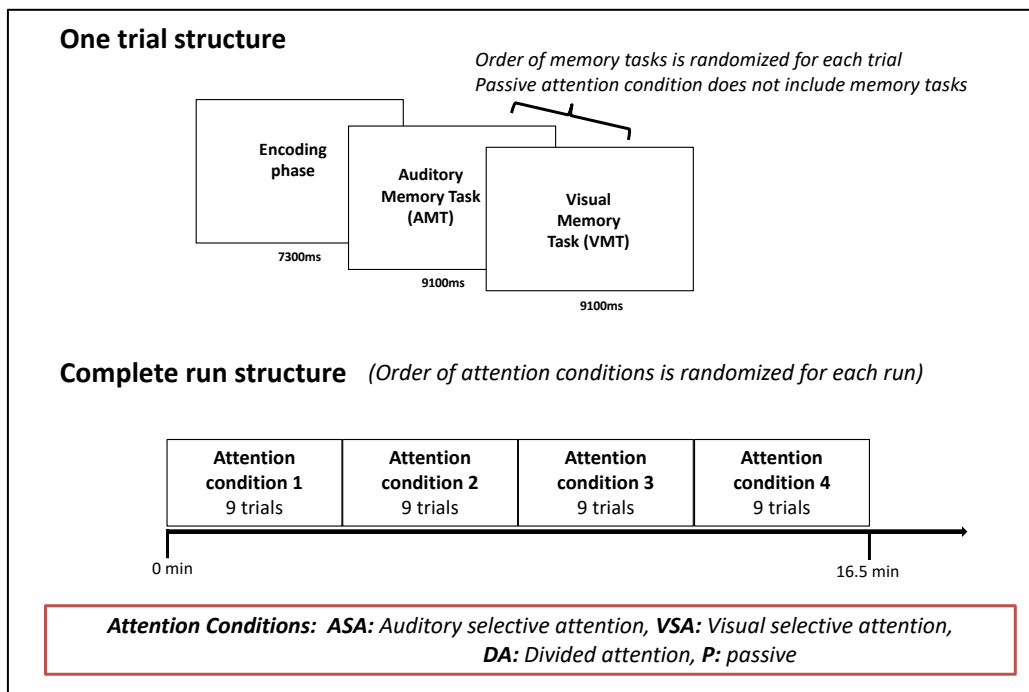


Figure 2: Experimental protocol. Order of attention conditions was randomized across participants.

5.3 Data acquisition

Structural and functional brain data were acquired with magnetic resonance imaging (MRI). MRI provides fine details of brain structure due to differences in magnetic properties of brain tissues (e.g., white matter versus gray matter). fMRI reveals the hemodynamic response associated with neural activity, and the foci of this activity are then superimposed on MRI images to determine the precise neuroanatomical structure(s) generating the neural activity. Thus, both MRI and fMRI reveal spatially well-defined neuroanatomical and functional loci undergoing structural and functional changes, for example due to musical training (Shahin, 2011).

5.3.1 Magnetic resonance imaging

Images were acquired at the Radiology Department of the Clínica Alemana de Santiago with a 3T Siemens Skyra scanner and a 20-channel head coil. Participants were prepared for MRI and were instructed to relax and keep still during image acquisition. When children were uncomfortable with staying alone in the MRI room, they were accompanied by one of their parents or myself during the scanning procedure. All participants were scanned on a Saturday ($n = 36$) or Sunday ($n = 4$) morning between 10 and 12 o'clock.

5.3.1.1 *Structural magnetic resonance imaging*

For each subject a structural T1-weighted scan (Voxel size: 1x1x1mm, Slices per slab: 176, FoV: 256mm, TR=2.53s, TE=2.19ms) and a structural T2-weighted scan (Voxel size: 0.5x0.5x1mm, Slices per slab: 176, FoV: 256mm, TR=3.2s, TE=412ms) was obtained. For 38 of 41 participants a structural diffusion-weighted scan (DTI) (Voxel size: 1.7x1.7x4.0mm, Slices: 29, Directions: 20, FoV: 220mm, TR=3.9s, TE=95ms) was obtained.

Data sets from 36 of our 40 participants (19 musically trained and 17 non-musically trained children) met criteria for high quality scans and were subsequently included in the Voxel-based morphometry (VBM) analysis. Data sets from 33 of our 38 participants (16 musically trained and 17 non-musically trained children) who had a DTI scan met criteria for high quality and scan stability and were subsequently included in the Tract-based spatial statistics (TBSS) analysis.

5.3.1.2 Functional magnetic resonance imaging

For each subject phase and magnitude fieldmaps (Voxel size: 2.7x2.7x2.3mm, Slices: 72, FoV: 208, TR=731ms, TE1=4.92ms, TE2=7.38ms) and a functional T2*-weighted gradient echo planar imaging scan (Voxel size: 3x3x3mm, Slices: 38, FoV: 220, TR=2.21s, TE=30ms) was acquired.

During functional T2*-weighted gradient echo planar imaging, our bimodal attention task (Figure 1 and Figure 2) was presented using Presentation Software (Neurobehavioral Systems). Auditory stimuli were presented over MRI-compatible headphones (Resonance Technology Inc., <http://www.mrvideo.com/>) and visual stimuli were presented on a screen located in the MRI room. The coil had a mirror attached, so that participants could see the screen where visual stimuli were displayed. Answers were given via button press on a keypad.

Data sets from 35 of our 40 participants (18 musically trained and 17 non-musically trained children) met criteria for high quality and scan stability with minimum motion correction (> 3mm displacement in any direction) and were subsequently included in the fMRI analysis (Table III).

	Musically trained children	Control children	
n	18	17	
Females	10	11	
	Mean \pm SD	Mean \pm SD	t value (p value)
Age (years)	12.2 \pm 0.8	12.2 \pm 0.8	-0.08 (0.53)
IQ	109.5 \pm 10.3	105.9 \pm 11.1	0.96 (0.17)
Parental education	3.8 \pm 1.7	4.1 \pm 1.6	-0.65 (0.74)

Table III: Demographics of participants included in the fMRI analysis.

5.4 Data analysis

5.4.1 Behavioral data

Behavioral data were studied using RStudio (R Version 3.1.2). Accuracy and reaction time for memory tasks were analyzed with a 2x3x2 mixed analysis of variance (ANOVA) to compare the main effects and interactions of group (between-subject factor: musicians, controls), attention condition (within-subject factor: ASA, VSA, DA) and memory task (within-subject factor: VMT, AMT). Whenever the assumption of sphericity was violated, the Greenhouse-Geisser correction for epsilon was applied. Interaction effects were further interrogated with pairwise *t*-tests. Bonferroni correction for multiple comparisons was applied where necessary. Alpha level of 0.05 was used for all statistical tests.

5.4.2 Magnetic resonance imaging

5.4.2.1 *Functional magnetic resonance images*

fMRI data were analyzed using FMRIB Software Library (FSL, version 5.0.10, <https://fsl.fmrib.ox.ac.uk/fsl>) (Jenkinson et al., 2012; Smith et al., 2004). Data preprocessing involved the following steps: motion correction including fieldmap unwarping (MCFLIRT), slice timing corrections, brain extraction (BET), spatial smoothing with a 6-mm FWHM Gaussian kernel, and high pass temporal filtering using Gaussian-weighted least-squares straight line fitting with $\sigma = 100.0$ s, and pre-whitening. The BOLD response was modeled using a separate explanatory variable (EV) for each attention condition (ASA, VSA, DA, P) and the memory tasks in each active attention condition (ASA-VMT, ASA-AMT, VSA-VMT, VSA-AMT, DA-VMT, DA-AMT). The design was convolved with a double gamma hemodynamic response function and temporal derivatives of each EVs time-course and motion correction parameters were included as additional nuisance regressors. Estimated beta maps for contrasts were normalized to MNI152 standard space using linear transformations (FLIRT) in two stages. First, functional images were aligned with the high-resolution T1 using boundary-based registration (BBR). Then the T1 was registered to the standard MNI atlas with a 12-degrees-of-freedom affine transformation. Second-level activation maps were calculated with FSL using mixed-effect model (FLAME1+2). All reported results are based on an initial uncorrected voxel-level threshold of $z > 3.1$ and cluster inference using a familywise error - corrected

threshold of $p < .05$ in accordance with actual fMRI analysis guideline recommendations (Eklund et al., 2016).

In the first-level analysis we modelled the encoding phase and the memory tasks for the active attention conditions. The Hillyard Principle (Hillyard et al., 1973) states that in order to assess the effects of directed attention, responses should be compared to the same physical stimuli while holding overall arousal level and task demands constant, such that all that differs is the focus of directed attention. Following this principle, we modelled the attention component of the encoding phases of the active attention conditions by subtracting the passive condition from the encoding phase of the other three attention conditions, resulting in the contrasts [ASA > P], [VSA > P] and [DA > P]. Visual and auditory memory tasks after the specific attention conditions were calculated as individual regressors: ASA-VMT, VSA-VMT, DA-VMT, ASA-AMT, VSA-AMT and DA-AMT.

Then we carried out three second-level analysis models. In the first one we explored for differences between groups in encoding phases and memory tasks. In the second one we added a regressor for the accuracy in the auditory memory task, in order to further investigate the three-way interaction effect that we found in the behavioral analysis. In a third model, we added a regressor for the time of musical training (years), in order to disentangle if the results obtained with the anterior model would be better explained by attentional bias or by a facilitation in the encoding of the auditory stimulus. Finally, we performed a conjunction analysis to determine the overlaps between (1) the contrasts that showed differences between musicians and controls in the encoding phases determined with the first model, and (2) the results of the second and third models.

Activation maps selected for figures were overlaid on a high-resolution brain image in MRICroGL or FSLeyes for visualization. Activation locations were confirmed using the Harvard-Oxford Cortical Structure Atlas. Data are presented following the Radiological convention (L, left; R, right) and coordinates are in MNI space.

5.4.2.2 Voxel-based morphometry (VBM) analysis of structural T1-weighted data

Structural T1-weighted data were analyzed with FSL – Voxel-based morphometry (VBM) (Douaud et al., 2007), an optimized VBM protocol (Good et al., 2001) carried out with FSL (Version 5.0.10). First, structural images were brain-extracted and grey matter-segmented before being registered to the

MNI152 standard space using non-linear registration (Andersson et al., 2007b). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Second, all native grey matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, voxelwise general linear model (GLM) was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space.

5.4.2.3 *Tract-based spatial statistics (TBSS) analysis of structural diffusion tensor imaging (DTI) data*

Diffusion tensor imaging (DTI) data were analyzed using tract-based spatial statistics (TBSS) (Smith et al., 2006) with FSL (Version 5.0.10). TBSS first aligns the fractional anisotropy (FA) images that were obtained from the DTI data to the brain-extracted structural T1. Then it aligns subjects' FA data into a common space using the FMRIB's nonlinear registration tool (FNIRT) (Andersson et al., 2007a), which uses a b-spline representation of the registration warp field. Next, it creates and thins a mean FA image to create a mean FA skeleton, which represents the centers of all tracts common to the group. It then projects each subject's aligned FA data onto this skeleton.

Voxel-wise statistical comparisons were then performed with FSL's Randomise tool (Winkler et al., 2014), using the "Threshold-Free Cluster Enhancement" (TFCE) option, with five thousand two-tailed Monte Carlo permutations. We specified a higher-level design matrix with an unpaired two group design. We utilized a significance threshold of $p = 0.05$ and all p-values were corrected for multiple comparisons. Analysis were performed to identify clusters with significantly different FA, radial diffusivity (RD) or mean diffusivity (MD) between groups.

6 Results

6.1 Musically trained children had an overall better performance on the memory tasks and the significant three-way interaction found between group, attention condition and memory task was given by the correct responses to the auditory memory task during the visual selective attention condition

Percent of correctly remembered stimuli and reaction times of correct responses for both groups for each memory task across attention conditions are shown in Figure 3 and Table IV respectively. Results were analyzed with a 2x3x2 mixed ANOVA with group, attention condition and memory task as factors as detailed in 5.4.1.

Behavioral results for correct responses to memory tasks showed a significant main effect of group ($F(1,33)=6.1$, $p = 0.019$). Overall musically trained children had a better performance on memory tasks than control children (Mus: mean=7.09, $SD=1.69$; Cont: mean=6.28, $SD=2.3$). They also showed that in both groups, attention condition significantly modulated the correct responses for memory tasks, with attended stimuli being better remembered than unattended stimuli ($F(3.1,102.3)=11.3$, $p[GG] = 0.0007$). In other words, melodies were better remembered in auditory selective attention and divided attention condition, whereas melodies were better remembered in visual selective attention and divided attention conditions. We found no difference among correct responses to auditory and visual memory task in the divided attention as compared to the respective selective attention condition. The three-way interaction that we found between group, attention condition and memory task ($F(3.1,101.6)=3.8$, $p[GG] = 0.046$) was given by the correct responses to the auditory memory task (AMT) in the visual selective attention condition (VSA) ($t = 3.0226$, $df = 28.005$, uncorrected $p = 0.00531$; Bonferroni-corrected $p = 0.032$). On average, musicians had 6.2 ($SD=1.6$) correct responses as opposed to controls, who had an average of 4.1 ($SD=2.4$) correct responses (Figure 3).

Behavioral results for reaction time of correct responses showed no main effect or interaction effects between group, attention condition and memory task. Overall mean reaction time was 809ms ($SD = 284ms$) (Table IV).

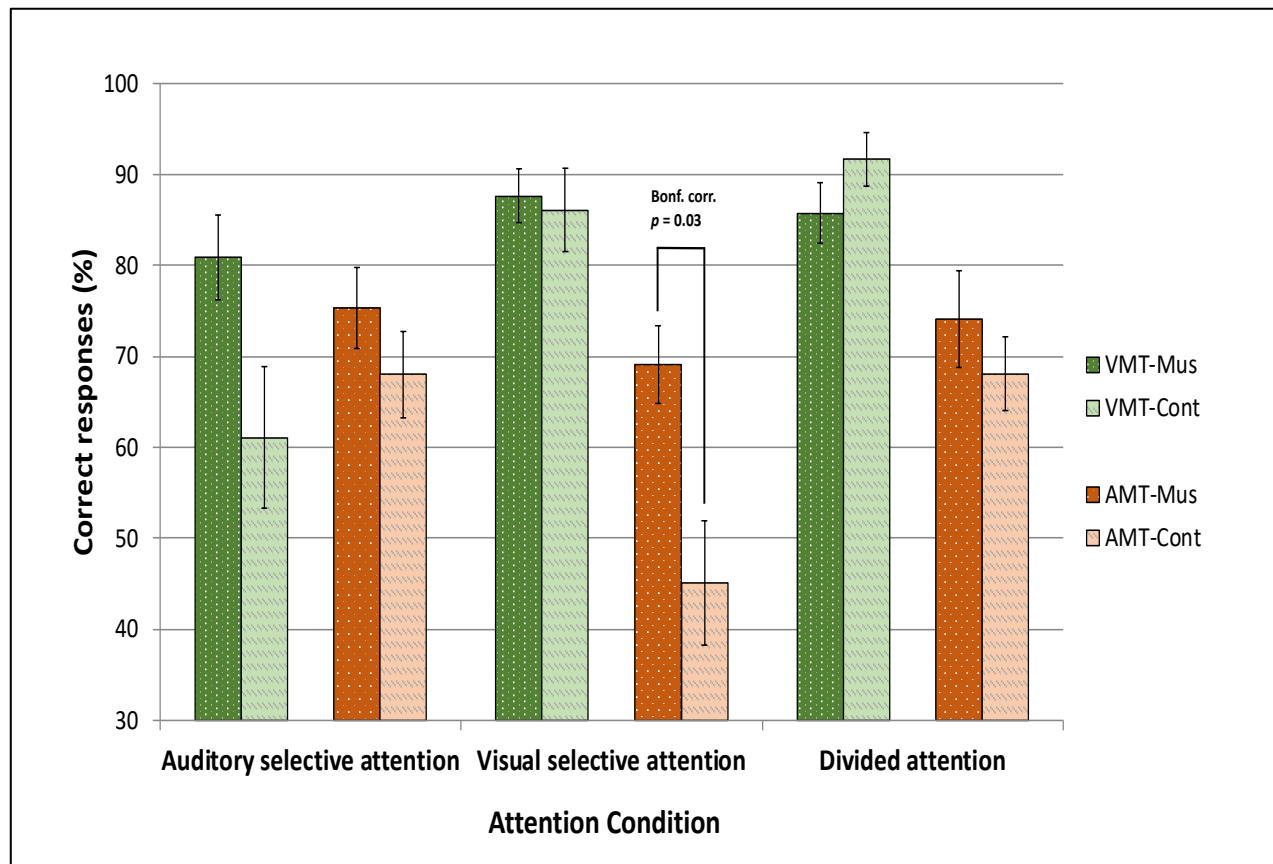


Figure 3: Accuracy for memory tasks after each encoding phase in the three active attention condition. Overall musically trained children had more correct responses than control children ($F(1,33)=6.1$, $p<.05$). The three way interaction effect between group, attention condition and memory task ($F(3.1,101.6)=3.8$, $p[GG]<.05$) was given by the correct responses to the AMT during the visual selective attention condition (Bonf. corr. $p = 0.03$). Error bars indicate standard error of the mean. VMT: visual memory task; AMT: auditory memory task; Mus: musically trained children; Cont: control children.

Attention condition before MT	VMT		AMT	
	Musicians	Controls	Musicians	Controls
	RT \pm SEM (ms)	RT \pm SEM (ms)	RT \pm SEM (ms)	RT \pm SEM (ms)
ASA	808.6 \pm 55.9	830.2 \pm 118.3	835.8 \pm 74.1	856.6 \pm 74.0
VSA	772.1 \pm 49.5	839.9 \pm 54.3	788.3 \pm 66.8	750.5 \pm 123.8
DA	810.8 \pm 52.7	777.1 \pm 61.4	755.7 \pm 47.4	765.4 \pm 67.7

Table IV: Reaction time for correct responses to memory tasks after each attention condition. There was no significant difference between reaction times. ASA: auditory selective attention; VSA: visual selective attention; DA: divided attention; MT: memory task; VMT: visual memory task; AMT: auditory memory task.

6.2 Musically trained children showed higher activation in areas involved in the fronto-parietal attention network and the thalamus in the encoding phase of all active attention conditions

In order to determine the neural activity underlying attention during the encoding phase we modelled our contrasts by subtracting the passive condition from the other three attention conditions. In line with our behavioral results that showed an overall better performance of musically trained children across attention conditions and memory tasks, whole brain analyses of encoding phase contrasts ([ASA > P], [VSA > P] and [DA > P]) showed a significantly greater activation for musically trained children as compared to control children (corrected $p < 0.05$) in areas related to attentional control.

For musically trained children the contrasts showed activation of a bilateral fronto-parietal network, including activation in dorsolateral prefrontal cortex (dlPFC), frontal eye-fields (FEF) and the supramarginal gyrus (SMG). There was also activation in subcortical structures such as the thalamus (corrected $p < 0.05$) (Figure 4). For control children, there was no significant activation in the [ASA > P] or [DA > P] contrast at our threshold level (corrected $p < 0.05$), whereas there was activation in the left middle frontal gyrus (MFG), the bilateral inferior division of the occipital cortex (OC) and the cerebellum in the [VSA > P] contrast (Figure 5).

When comparing contrasts across groups, results showed significant activation for musically trained children as compared to control children in all three contrasts (corrected $p < 0.05$) (Figure 6). Musically trained children showed higher activation in regions including bilateral dlPFC, medial premotor area, right dorsal precentral gyrus (pre-CG), left SMG, bilateral posterior division of the cingulate cortex (pCC) and bilateral thalamus for the [ASA > P] contrast; left dlPFC, right superior parietal lobe (sPL), bilateral pCC and bilateral thalamus for the [VSA > P] contrast; and bilateral dlPFC, left sPL, left anterior division of the cingulate cortex (ACC), left pCC and bilateral thalamus for the [DA > P] contrast. The conjunction analysis for the contrasts of Musicians over controls for the three contrasts showed activation in the left pCC, the left ACC, the left dlPFC and the left sPL (Figure 7). The opposite comparison of control children over musically trained children resulted in no activation at our threshold level (corrected $p < 0.05$).

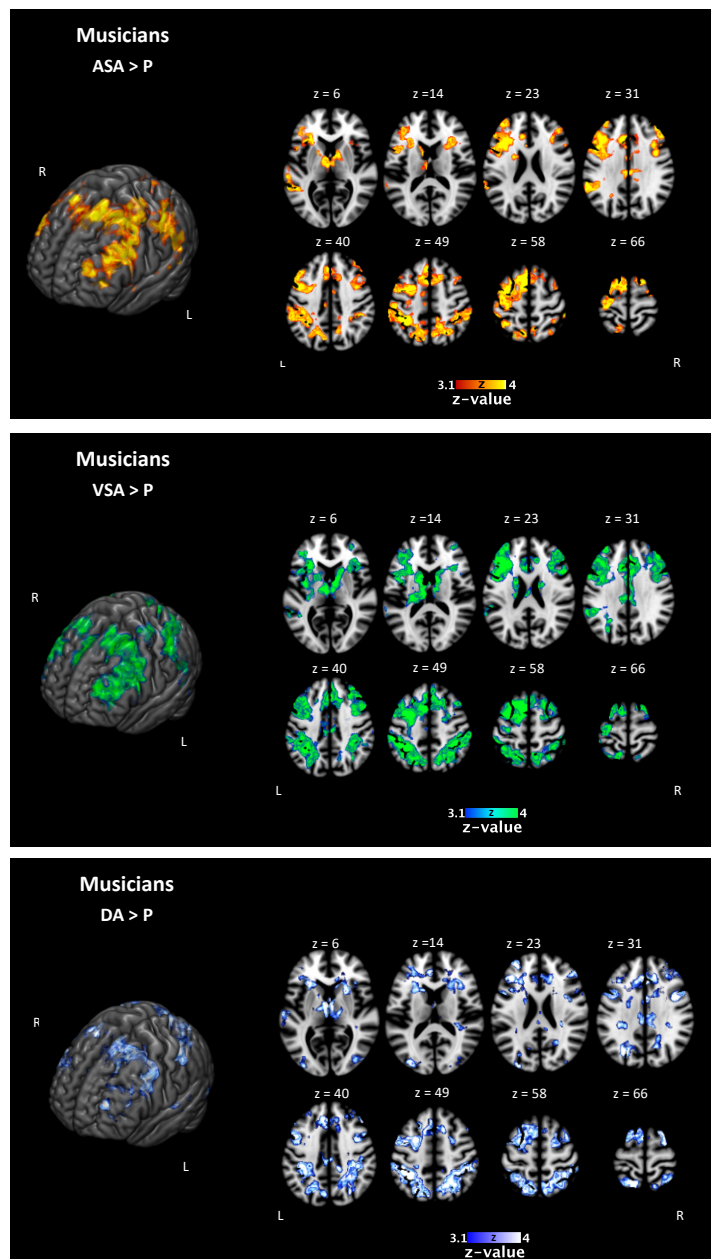


Figure 4: Whole brain activation during encoding phase for the contrasts [ASA > P], [VSA > P] and [DA > P] in musically trained children (corrected $p < 0.05$).

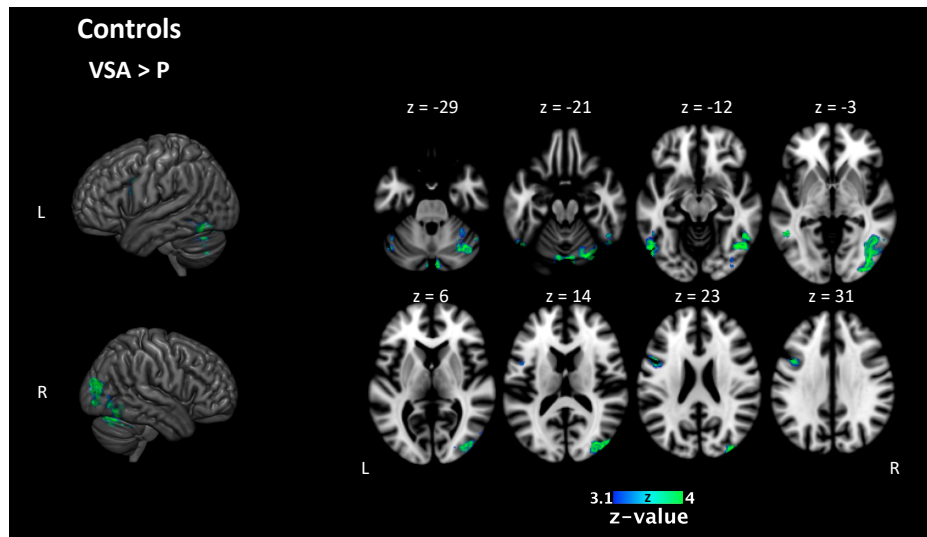


Figure 5: Whole brain activation during encoding phase for the contrast [VSA > P] in control children (corrected $p < 0.05$).

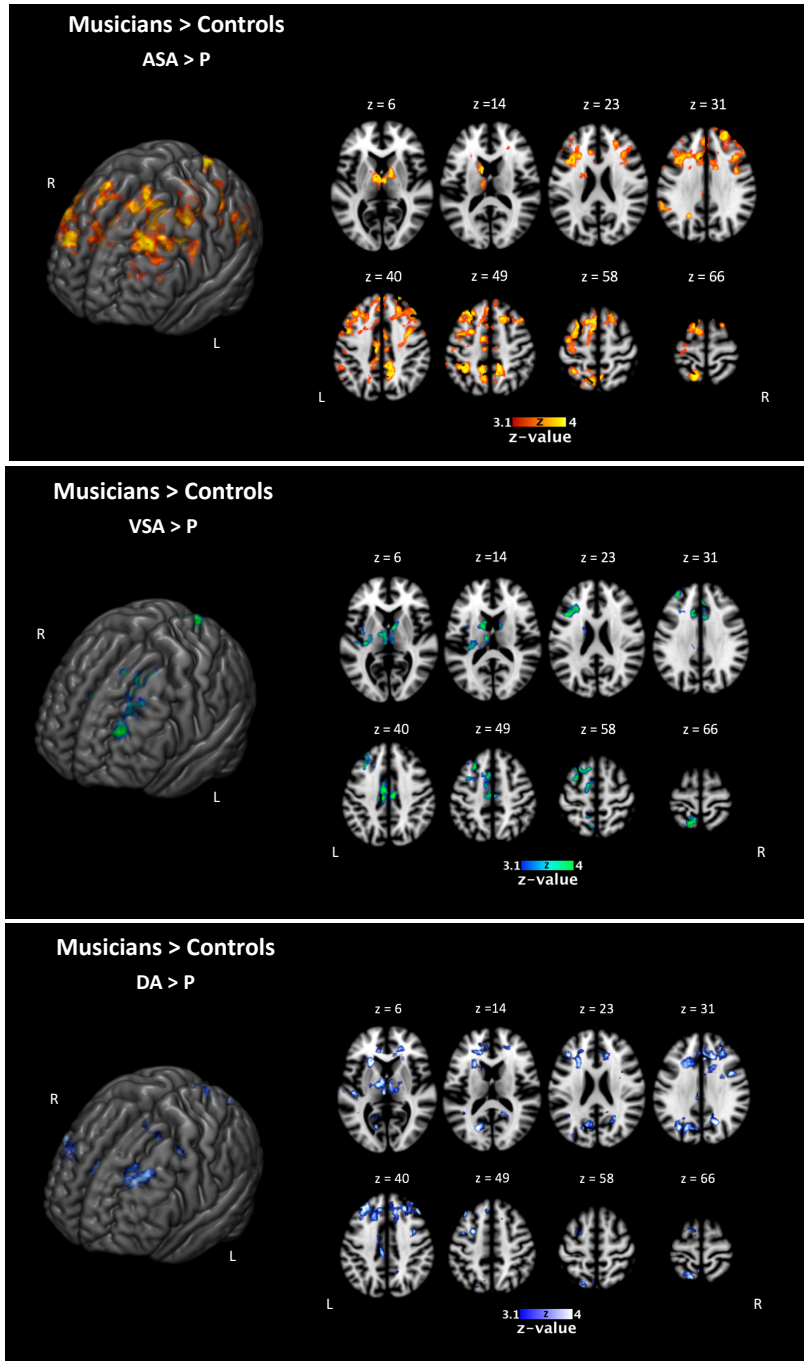


Figure 6: Two-sample comparison of musically trained children over control children during encoding phase for the contrasts [ASA > P], [VSA > P] and [DA > P] (corrected $p < 0.05$).

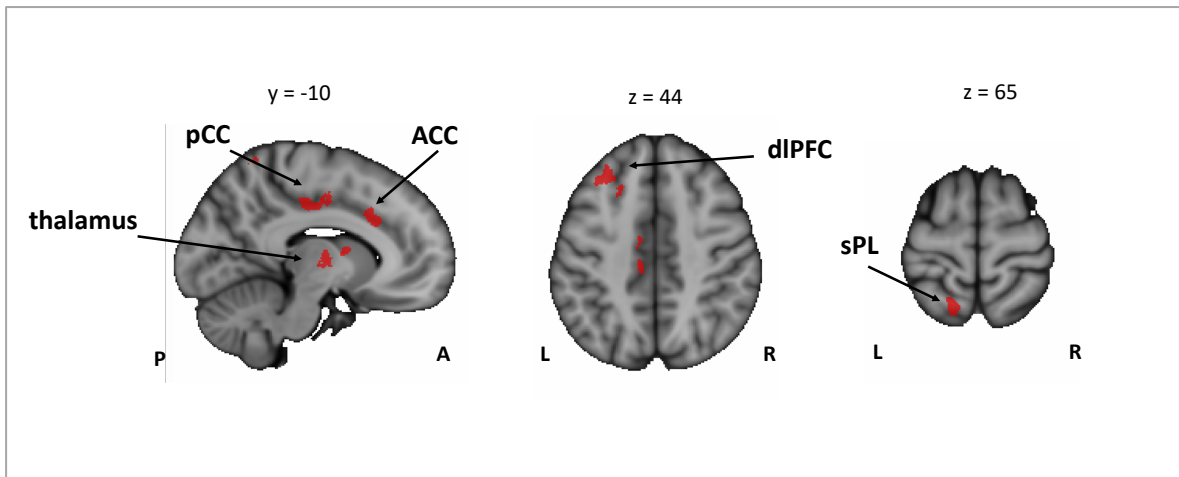


Figure 7: Conjunction analysis between the activation Musicians > Controls for the encoding phase of the contrasts [ASA > P], [VSA > P] and [DA > P]. VSA: visual selective attention; ASA: auditory selective attention; DA: divided attention; P: passive; pCC: posterior cingulate cortex; ACC: anterior cingulate cortex; dlPFC: dorsolateral prefrontal cortex; sPL: superior parietal lobe.

In order to determine the neural activity underlying memory retrieval during the memory tasks, visual and auditory memory tasks were modelled for each attention conditions as ASA-VMT, VSA-VMT, DA-VMT, ASA-AMT, VSA-AMT and DA-AMT. Interestingly, here we did not find differences among groups. Figure 8 shows an example of the activation elicited during the visual and auditory memory task after auditory selective attention encoding phase.

Taken together, our results suggest that the overall better performance of the musically trained children in our bimodal attention task seems to be driven by higher activation of attention control related brain areas (e.g. dlPFC and SPL) during encoding phase in musically trained children as compared to controls in all active attention conditions (Figure 6 and Figure 7).

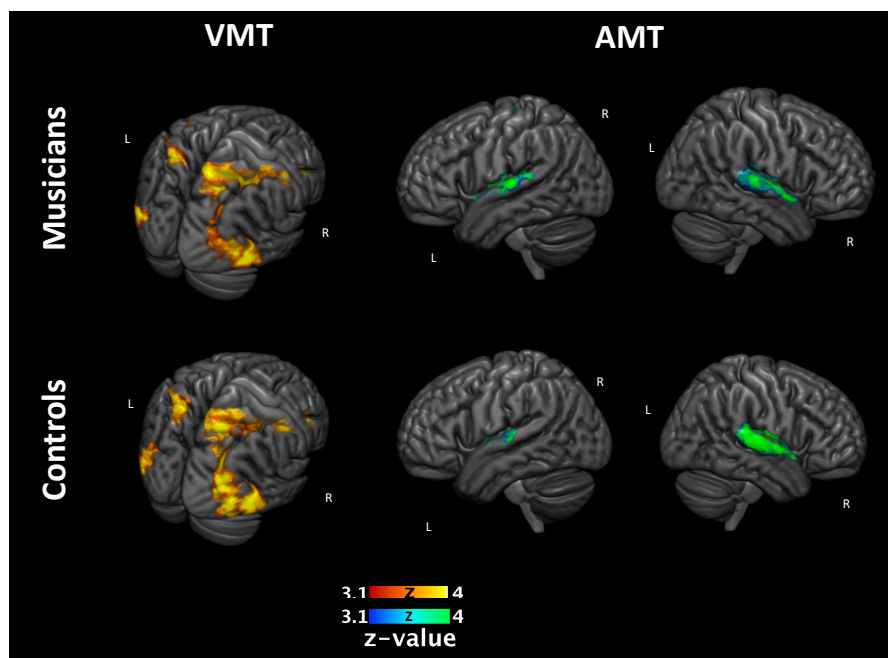


Figure 8: Whole brain activation for musicians and controls during memory tasks after auditory selective attention encoding phase in musically trained and control children (corrected $p < 0.05$). No differences among groups were found for the memory tasks. *VMT: visual memory task; AMT: auditory memory task.*

6.3 Activity in left SMG and left IFG facilitated the encoding of auditory stimuli in auditory working memory in musically trained children

In order to investigate the three-term interaction effect found in our behavioral analysis, we correlated the activation in the encoding phase of the [VSA > P] contrast with the correct responses of each subject in the auditory memory task after the VSA condition (Second second-level analysis model described in 5.4.2.1). When comparing the results among groups, we found a higher activation of the left SMG, the supplementary motor area (SMA), the ACC, the left superior IFG and the left frontal pole in musically trained children as compared to controls (Figure 9). This effect could be given by (1) an attention bias that musically trained children have for auditory stimuli despite being in the VSA condition, or (2) it could be that musical training provides a general facilitation for the encoding of auditory stimuli. If the latter were true, a similar modulation should be found when musically trained children pay attention to auditory stimuli (ASA) and this modulation should correlate with the years of musical training (Third second-level analysis model described in 5.4.2.1). In order to test this, we revised if there was an overlap between the previous result (Figure 9) and the activity that correlated with the years of musical training in the musically trained group during the encoding phase of the [ASA > P] contrast (Figure 10). We found two points of overlap: the left IFG (specifically the pars opercularis) and the left SMG (Figure 11).

Taken together, our results suggest that musical training facilitates the encoding of auditory stimuli in auditory working memory and that this facilitation relies on the left IFG and the left SMG in musically trained children.

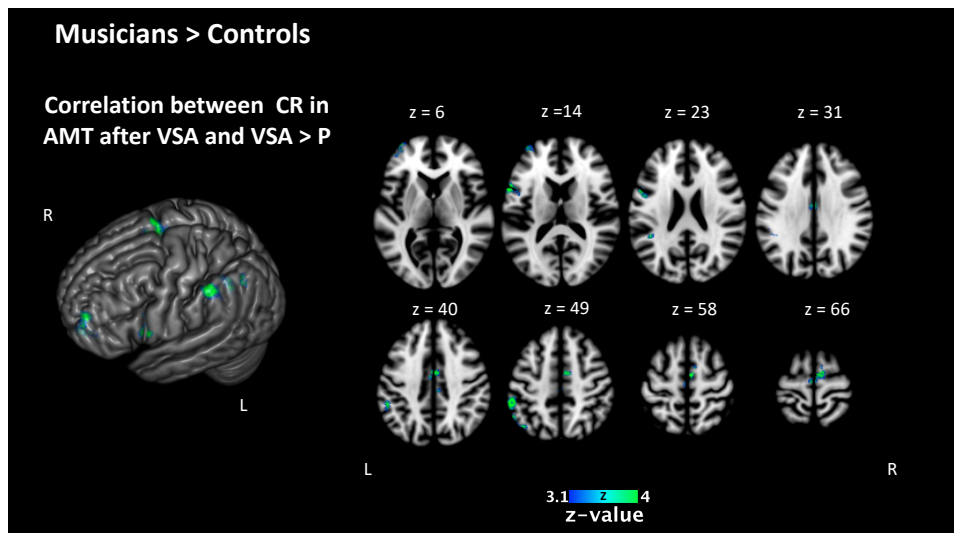


Figure 9: Two-sample comparison of musically trained children over control children for the correlation between the activation in the encoding phase of the [VSA > P] with the correct responses of each subject in the auditory memory task after the VSA condition (corrected $p < 0.05$). VSA: visual selective attention; P: passive; CR: correct responses; AMT: auditory memory task.

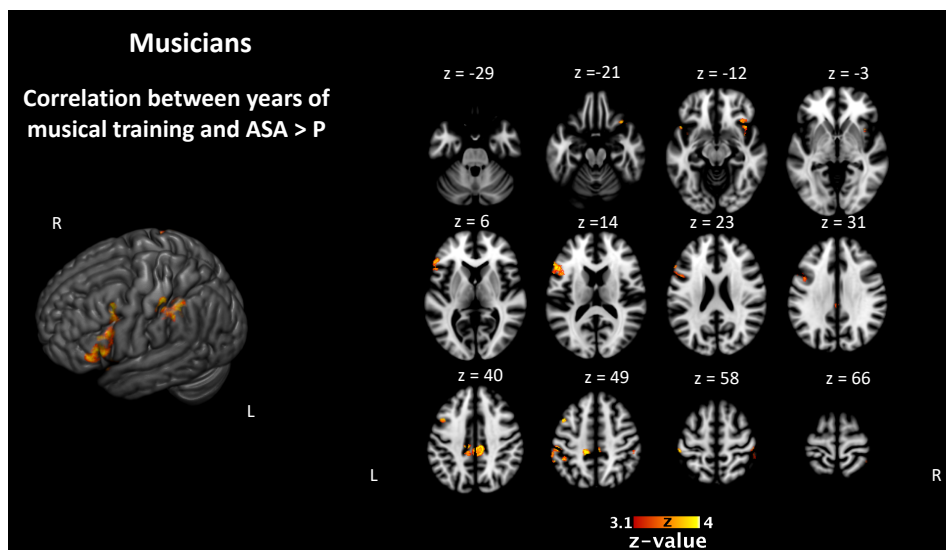


Figure 10: Activity that correlated with the years of musical training in the musically trained group during the encoding phase of the [ASA > P] contrast (corrected $p < 0.05$). VSA: visual selective attention; P: passive.

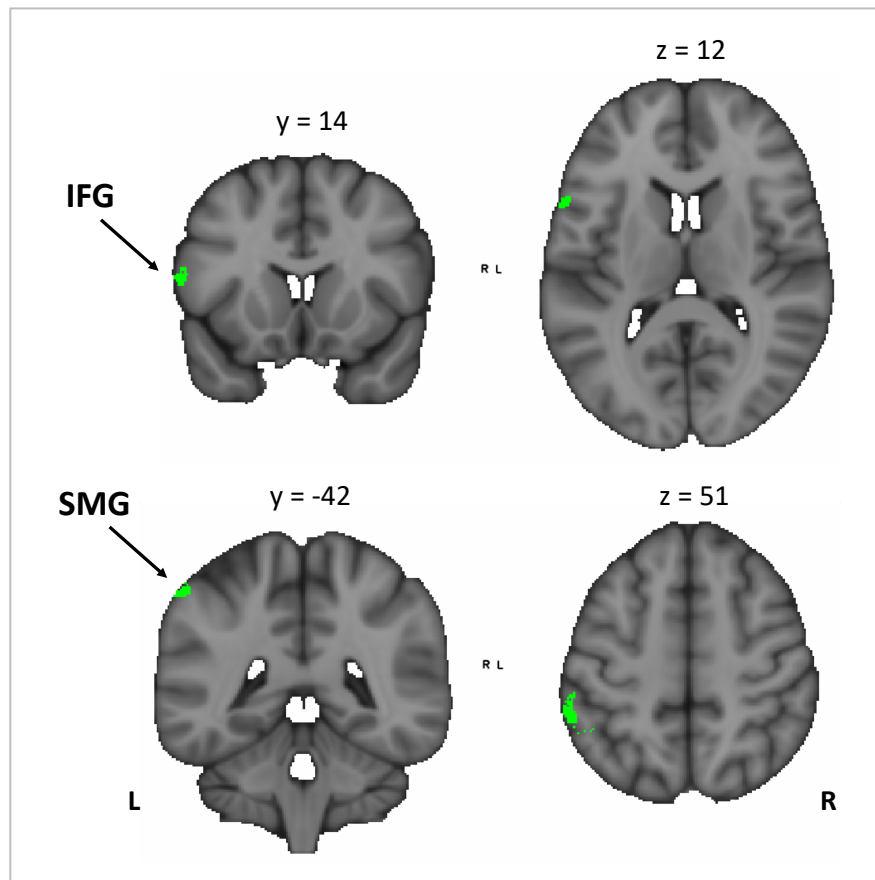


Figure 11: Conjunction analysis between the correlation between the activation in the encoding phase of the [VSA > P] with the correct responses of each subject in the auditory memory task after the VSA condition and the correlation between the years of musical training in the musically trained group with the encoding phase of the [ASA > P]. VSA: *visual selective attention*; ASA: *auditory selective attention*; P: *passive*. IFG: *inferior frontal gyrus*; SMG: *supramarginal gyrus*.

6.4 No structural differences in gray matter (VBM) nor white matter (DTI-TBSS) were found between groups

In order to investigate if there were structural differences that could also account for the behavioral differences found among groups, we performed two different analysis: (1) Voxel-based morphometry (VBM) on T1-weighted data, which allowed us to investigate whether there were voxel-wise differences in local grey matter volumes between groups, and (2) tract-based spatial statistics on diffusion tensor imaging (DTI) data, which allowed us to investigate whether there were differences in white matter (fractional anisotropy) between groups. Details of each analysis are described in 5.4.2.2 and 5.4.2.3 respectively. None of our structural analysis showed significant differences between groups (Figure 12 and Figure 13).

Taken together, our results suggest that the behavioral differences that we found between groups in our bimodal attention task are not due to structural differences among groups.

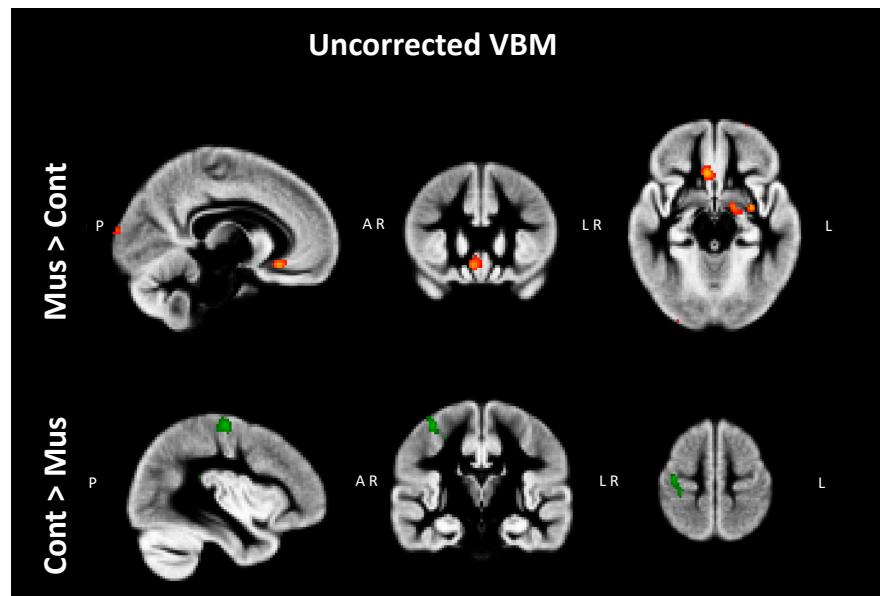


Figure 12: Uncorrected voxel-based morphometry results displayed for the contrasts Mus > Cont and Cont > Mus. These differences do not survive corrections, so there are no significant differences in local gray matter volumes between groups. *Mus: musically trained children; Cont: control children.*

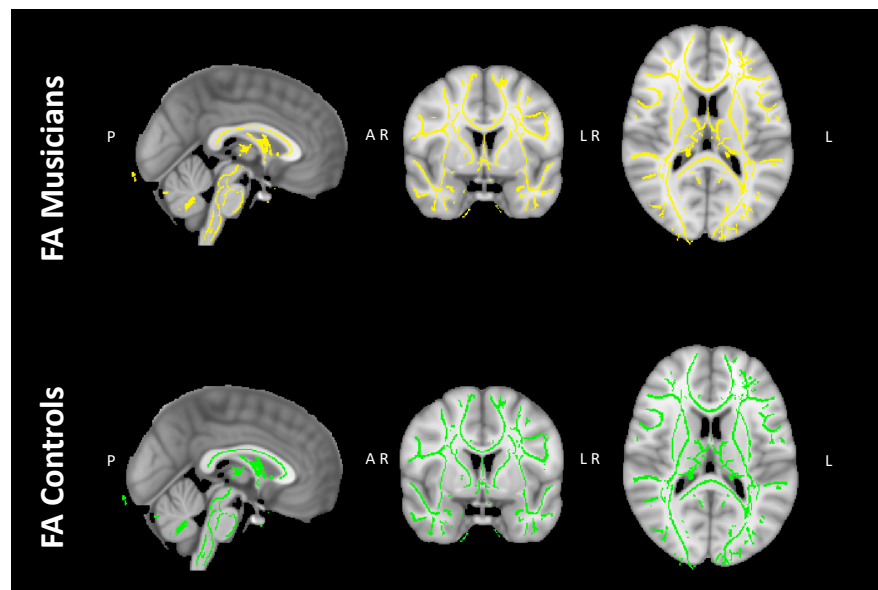


Figure 13: Mean Fractional Anisotropy (FA) skeleton of each group. There are no significant differences of FA between groups.

7 Discussion

In this thesis, we sought to investigate goal-directed selective and divided attention and subsequent memory for simultaneous bimodal (auditory/visual) stimuli in children who play musical instruments. In particular, we were interested in investigating the neural correlates underlying these functions in musically trained children as compared to control children. Our main hypothesis was that playing a musical instrument trains selective and divided attention in children, and that this would be reflected in their neural correlates of attention and memory. To test our hypothesis, we designed and completed a cross-sectional study in which 41 children aged 10 to 13 (20 musically trained children (3.7 ± 1.3 years of training); 21 control children) solved a bimodal (auditory/visual) attention task (Figure 1 and Figure 2) while their brain activity was being measured with functional magnetic resonance imaging. Both groups were matched for gender, age, intelligence coefficient (WISCIII) and socioeconomic status (educational level of both parents) (Table II).

Our behavioral results (accuracy on the memory tasks after encoding phase in active attention conditions) showed that musically trained children had an overall better performance on both of the memory tasks as compared to controls (Figure 3). These results did not confirm our first specific hypothesis, which stated that musically trained children would have a better performance on the auditory memory task in the auditory selective attention and divided attention conditions. Importantly though, our results point in the same direction as other studies that have found that musicians have a better performance both in auditory and visual memory tasks (Rodrigues et al., 2013; Slevc et al., 2016; Talamini et al., 2016). Several studies have proposed that particularly reading scores and playing in an orchestra seems to have an impact in the visual attentional and memory skills of musicians (Land & Furneaux, 1997; Rodrigues et al., 2007, 2013). Since all of our musically trained participants read music scores and played in an ensemble, it is plausible that this may have contributed to the overall better performance of the musically trained children in both memory tasks.

In line with our behavioral results, our functional brain imaging results showed that musically trained children had higher activation in the attentional control related brain areas (e.g. dlPFC and superior PL) (Maurizio Corbetta & Shulman, 2002) in the encoding phase of all three active attention conditions (auditory selective, visual selective and divided attention) when compared to control

children (Figure 6 and Figure 7). These results did confirm our second specific hypothesis, which stated that musically trained children would have a higher activation of the fronto-parietal attention control network during the auditory selective attention and divided attention conditions. Additionally, this higher activation was also present in the visual selective attention condition. Musically trained children also showed significantly higher activation of the thalamus in all active attention conditions as compared to controls. The thalamus is important for sensory processing and integration (Cappe et al., 2009; McCormick & Bal, 1994), language processing (Crosson, 2013) and memory functions (Kopelman, 2015), and it is part of the subcortical structures that are associated with the salience attention network, which plays a major role in cognitive control (Halassa & Kastner, 2017; Peters et al., 2016). A recent study also showed that the functional connectivity of the thalamocortical network is reorganized in musicians (Tanaka & Kirino, 2017), showing that auditory areas are more strongly connected with the left thalamus in musicians as compared to controls. Our results also expand on the results obtained by Pallesen et al. (2010), who showed that the cognitive control network was enhanced during auditory working memory in musicians. Taken together, our results suggest that playing a musical instrument boosts the functioning of the brain networks that underlie selective and divided attention for both auditory and visual stimuli, and that this subserves the better memory capacity for auditory and visual stimuli shown by musically trained children in our task.

A second behavioral result that we found regarding accuracy on the memory tasks was a three-way interaction between the factors group, attention condition and memory task. This interaction was given by the group differences in the correct responses to the auditory memory task (AMT) after the visual selective attention (VSA) condition, with the musically trained children showing significantly better performance than control children (Figure 3). This result shows that even though children were instructed to pay attention only to the visual stimuli in this condition, musically trained children were still able to encode and remember the auditory stimuli that were presented during the encoding phase far better than control children. When we correlated the brain activity in the encoding phase of VSA (contrast [VSA > P]) with the correct responses to the AMT after this attention condition, we found significant differences among groups, with musicians showing higher activation in the left SMG among others (Figure 9). This behavioral effect could have been given by (1) an attention bias that musically trained children have for auditory stimuli despite being in the

VSA condition, or (2) it could be that musical training provides a general facilitation for the encoding of auditory stimuli. We reasoned that if the latter were true, a similar modulation should be found when musically trained children pay attention to auditory stimuli (ASA) and this modulation should correlate with the years of musical training. In order to test this, we checked if there was an overlap between the previous result (Figure 9) and the activity that correlated with the years of musical training in the musically trained group during the encoding phase of the [ASA > P] contrast (Figure 9). We found two points of overlap: the left IFG (specifically the pars opercularis) and the left SMG (Figure 11), which are both part of the phonological loop.

In general, the IFG, specifically Broca's Area, is known to be part of the language network and is involved in the perception and vocalizations of speech (Aboitiz, 2017). It has also been suggested that the IFG contributes to memory formation (Tang et al., 2018). Importantly, it has been shown that this area is a core structure that is involved in both tonal and verbal auditory working memory in musicians and non-musicians (Katrin Schulze et al., 2011). On the other hand, it has been shown that musicianship seems to have an impact on the structure of the left IFG. Abdul-Kareem et al. (2011) found that increased gray matter volume of left pars opercularis in male orchestral musicians correlated positively with years of musical performance. One could speculate then that our functional finding that subserved auditory memory encoding in our musically trained group could eventually lead to increased gray matter in this area.

On the other hand, the left SMG has been shown to participate in pitch memory (Ellis et al., 2013; Gaab et al., 2003). Notably, research using transcranial direct current stimulation (tDCS) (Schaal, Pollok, & Banissy, 2017; Vines, Schnider, & Schlaug, 2006) and transcranial magnetic stimulation (TMS) (Schaal et al., 2015) have implied that the left SMG is causally involved with pitch memory processing. Another recent study that included cross-sectional and longitudinal data also showed that the left SMG is involved in music processing in musically trained children and adults (Ellis et al., 2013). Participants in Ellis et al. (2013) solved a same/different melodic and rhythmic discrimination task. Similar as in our results, they found that activation in the left SMG was related to cumulative hours of musical practice in both tasks. Our results suggest that musical training facilitates the encoding of auditory stimuli in auditory working memory and that this facilitation relies on the left IFG and the left SMG in musically trained children.

Interestingly, the IFG and SMG that we found to be involved in auditory memory encoding in our musically trained group, have also been shown to be involved in visual stimuli processing. For example, Broca's area in the IFG has been shown to be activated to a greater extent by visually presented sentences when compared with spoken sentences (Carpentier et al., 2001), and the SMG has been causally involved in visual word recognition (Stoeckel et al., 2009). These results suggest that it is plausible that the increased functioning of these areas in musicians could eventually impact their visual processing. Effectively, it has also been found that Broca's Area supports enhanced visuospatial cognition in professional orchestral musicians (Sluming et al., 2007).

Given that previous work has shown that structural brain differences can be found when comparing musicians to non-musicians (Gaser & Schlaug, 2003; Habibi et al., 2017; Herholz & Zatorre, 2012), our third specific hypothesis stated that functional changes in attention and memory would also be reflected in structural changes, with musicians showing more gray matter in prefrontal regions (VBM) and more left than right asymmetry in the superior longitudinal fasciculus (DTI) than controls. Our results did not confirm this hypothesis. In our study, gray matter VBM analysis and white matter TBSS analysis did not show any significant differences among groups (Figure 12 and Figure 13). This could be due to the fact that the amount of training is not yet enough to produce detectable white or gray matter changes or that the effect is not so big, meaning that we would need more children to see a difference. Considering that most studies that have found structural differences among musicians and non-musicians have been performed on adults, and mostly on professional musicians who have many years of practicing, we are more inclined to think that it is because of the former. It is also important to keep in mind that we looked at a developmental period, so it could also be that structural changes are confounded by this fact.

Taken together, our results suggest that playing a musical instrument has a broad impact on goal-directed attention and cognitive control networks. Our study shows that better performance of musically trained children in auditory and visual working memory was guided by a higher activation of attention (e.g. dlPFC and superior PL) and subcortical cognitive control areas (e. g. thalamus) in musically trained children as compared to control children. Our findings also suggest that the better performance of musically trained children in our attention task is not only due to improved allocation of attentional resources, but also due to facilitated encoding of auditory stimuli given by years of training that depends on the left IFG and left SMG, which are part of the phonological loop.

Based on the above discussed results, we propose that two distinct neural mechanisms, a domain-general and a domain-specific one, contributed to the enhancement of auditory and visual working memory in musically trained children (Figure 14).

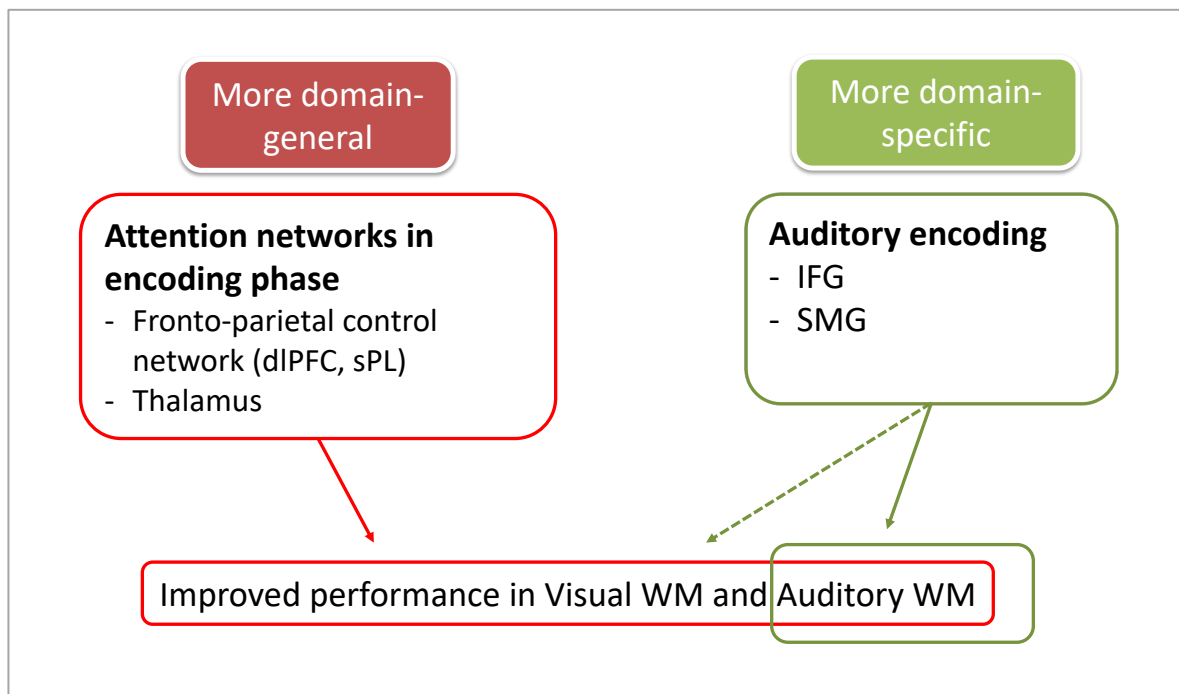


Figure 14: Mechanistic scheme that shows the two distinct neural mechanisms that seem to underlie the improvement of visual and auditory working memory in musically trained children. Continuous arrows indicate the results obtained in this research, the dotted arrow indicates that this brain network could also potentially support visual WM (see discussion). *WM: working memory; dlPFC: dorsolateral prefrontal cortex; sPL: superior parietal lobe; IFG: inferior frontal gyrus; SMG: supramarginal gyrus.*

Importantly, this mechanistic framework can help to interpret the impact of musical training on executive functions across lifespan, including recent findings that have shown that the lifelong playing of a musical instrument could have a positive influence on auditory performance and cognitive functioning in older adults (Grassi et al., 2017; Moussard et al., 2016; Strong & Mast, 2018).

8 Conclusion

This research contributed new knowledge to better understand the neural mechanisms that underlie the better performance of musically trained children on attention tasks. Our results permitted to gain new insight into the neurobiology of attentional control and memory mechanisms that underlie enhanced bimodal selective and divided attention skills and also auditory and visual working memory skills in musically trained children. Our results strongly suggest that two distinct neural mechanisms, one domain-general (fronto-parietal control network) and one domain-specific (IFG and SMG, the phonological loop) respectively, played a role in the better performance of musically trained children on our task. Our proposed mechanistic framework can help to interpret the effects of musical training on executive functions across lifespan.

Our results could be important to embrace and expand educational policies on music training. We hope that our findings will help to maintain and support community music programs that seek to encourage, inspire and motivate young people through music, such as the “Fundación de Orquestas Juveniles e Infantiles de Chile”, founded in 2001. This program provides comprehensive, tuition-free music education and social support to youth and seeks to deliver development opportunities through music to children and young people in Chile. We also hope that our research will convince policy makers of the importance of music lessons in general school curricula.

Our results are also important public health policies. Importantly, our results suggest that musical training could be used as a non-pharmacological intervention strategy for children with attentional problems.

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