JYVÄSKYLÄ STUDIES IN HUMANITIES
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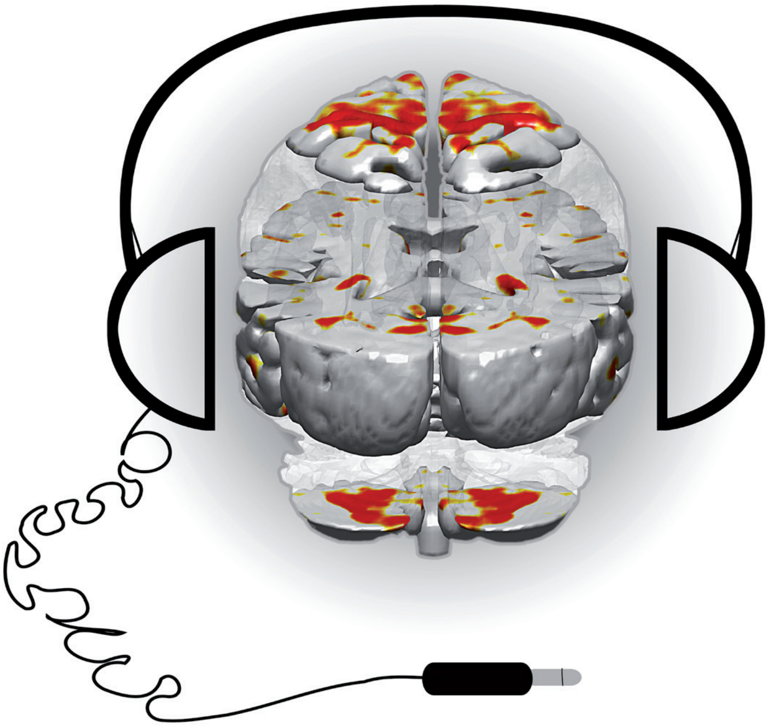
Iballa Burunat Pérez

Brain Integrative Function Driven by Musical Training During Real-World Music Listening



JYVÄSKYLÄN YLIOPISTO

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UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ 2017

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A mis padres, Rochi y José Antonio

I never was aware of any other option but to question everything
—N. Chomsky

ABSTRACT

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The present research investigated differences in the brain dynamics of continuous, real-world music listening between listeners with and without professional musical training, using functional magnetic resonance imaging (fMRI).

A replication study was aimed at validating the reliability of the naturalistic approach to studying brain responses to music, wherein the brain signal and the acoustic information extracted from the musical stimulus were correlated. After a successful replication, a series of three studies dealt with differences in integrative brain function during music listening between musicians and nonmusicians. Findings (a) emphasized the crucial role of the distinctive postural and kinematic symmetry in instrument playing on the symmetry of brain responses to music listening, evidencing a crossmodal transfer of symmetry from sensorimotor to perceptual processing systems; (b) provided novel evidence for increased cerebello-hippocampal functional coupling in musicians as a function of musical predictability compared to nonmusicians, likely mediated by action simulation mechanisms; (c) highlighted differences in pulse clarity processing between groups and uncovered an associated action-perception network overlapping with areas previously observed to tightly interact in rhythm processing.

In conclusion, the present research findings, obtained using a naturalistic auditory stimulation paradigm, will advance the understanding of brain integrative function during real-world music listening, in listeners with and without musical expertise. Particularly, this thesis has implications for a better understanding of training-induced crossmodal reorganization. The new evidence brought by the present findings will hopefully guide the generation and development of future testable hypotheses.

Keywords: functional magnetic resonance imaging (fMRI), functional connectivity, functional symmetry, musical training, predictive listening, Independent Component Analysis (ICA), pulse clarity.

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FOREWORD

The present PhD work was carried out from January 2013 to September 2016 at the Finnish Centre for Interdisciplinary Music Research. The diversity of questions and approaches here contained documents a long journey and its many detours resulting from the reciprocal feedback between unpredicted outcomes and initial hypotheses. My principal companion in this journey has been professor Petri Toiviainen, a true Renaissance man of insatiable, contagious curiosity, to whom I shall always be indebted for his exceptional mentorship, encouragement, constant availability, intellectual stimulation, perceptive observations, constructive criticism, and, most of all, his trust in me. You have taught me how good experimental work is done, allowing me to grow as a researcher (and as a better cook, as it appears). It has been a pleasure to overcome the challenges together. I have only phenomenal memories from these past years. For you I shall always carry a strong respect and affection.

I extend my very profound gratitude to professor Elvira Brattico for her invaluable, patient guidance, and support throughout the course of my PhD as my second supervisor, and for providing access to a rich dataset to explore, making all of this possible.

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This section provides an opportunity to express my gratitude and give credit to those indispensable ones, whom I owe in other ways. Bear with me.

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Dedico esta tesis a mis padres Rochi Pérez y José A. Burunat, un equipo singular: me facilitasteis las herramientas —tangibles e intangibles— para ser libre y embarcarme en mi propio camino. Ni con música ni con palabras puedo transmitir el bello sentimiento de ser hija vuestra. A dos seres fascinantes, mi *sistercita* Gisela Burunat y mi sobrina Elsa Burunat: aunque lejos, siempre os siento cerca, porque os llevo en mi piel.

To those who know me and do not know me, who have inspired me to be free in the pursuit of my own path. With all of you behind my shoulders, I never had it that hard.

Jyväskylä 5.12.2016
Iballa Burunat Pérez

FIGURES

CONTENTS

LIST OF PUBLICATIONS INCLUDED IN THIS THESIS

The following scientific articles referred as I-IV are summarized in this thesis. For all papers, the author was the principal contributor in preprocessing the fMRI data, performing the statistical analyses, interpreting the results, and writing the manuscript text as well as the responsible for the preparation of tables, plots and figures.

I Burunat, I., Toiviainen, P., Alluri, V., Bogert, B., Ristaniemi, T., Sams, M., & Brattico, E. (2016). The reliability of continuous brain responses during naturalistic listening to music. NeuroImage, 124, 224–231. doi:10.1016/j.neuroimage.2015.09.005.

II Burunat, I., Brattico, E., Puoliväli, T., Ristaniemi, T., Sams, M., & Toiviainen, P. (2015). Action in Perception: Prominent Visuo-Motor Functional Symmetry in Musicians during Music Listening. PLOS ONE, 10(9), e0138238. doi:10.1371/journal.pone.0138238

III Burunat, I., Brattico, E., Hartmann, M., Vuust, P., Särkämö, T., & Toiviainen, P. (under review). Music training predicts cerebello-hippocampal coupling during music listening.

IV Burunat, I., Tsatsishvili, V., Brattico, E., & Toiviainen, P. (under review). Coupling of action-perception brain networks during rhythm processing: Evidence from region-of-interest-based independent component analysis.

1 INTRODUCTION

> *Everybody knows that the ability of a pianist […] is unreachable for the untrained human, as the acquisition of new skills […] requires many years of mental and muscular gymnastics. To fully understand this complex phenomenon, it is necessary to accept that, in addition to the strengthening of pre-established organic pathways, new pathways are created by means of branching and progressive growth of dendritic ramifications and nerve endings.*
>
> —S. Ramón y Cajal, *Textura del Sistema Nervioso del Hombre y los Vertebrados*
> (translated by the author)

Music provides an invaluable framework for attempting to understand the human brain. In this way, the study of the brain and the study of music can be mutually revealing (Zatorre, 2005). Music is not only a universal constant in human societies, but it is also old in evolutionary terms (Wallin & Merker, 2001). However, because only a minority of individuals develop music-related expertise through years of sensory-motor training—often with an early onset in life—music has a privileged role in the study of brain adaptation (Peretz & Zatorre, 2003).

The growing interest in studying both the brain mechanisms involved in processing music in humans and the impact of musical training on cerebral and cerebellar function, has materialized over the last twenty years in a scientific body of evidence that supports the existence of structural and functional cerebral characteristics in musicians. These characteristics seem to generally correlate with the intensity and onset age of musical activities, thus supporting the hypothesis that structural and functional neuroplastic processes emerge as a consequence of long-term musical training. For this reason, musicians represent an ideal population to study experience-driven brain adaptation by investigating the relationship between brain dynamics and behaviour.

Comparable to how physical exercise impacts and shapes the body, music is, in words of Kraus and Chandrasekaran (2010), *a resource that tones the brain for auditory fitness*. Thus, music training primes the brain for processing musical sounds, thereby rendering the musician's brain a model of neuroplasticity (Peretz & Zatorre, 2005; Zatorre, 2005; Zatorre, Chen, & Penhune, 2007).

Why music training as a model to understand neuroplasticity?

> *SOCRATES: And therefore, I said, Glaucon, musical training is a more potent instrument than any other, because rhythm and harmony find their way into the inward places of the soul, on which they mightly fasten.*
>
> —Plato, *The Republic*

First, the differences between natural and artificial training regimes should be stressed. While natural training regimes (e.g., musical training, video games and athletics) involve simultaneous engagement of tasks which demand highly parallel processing across domains (Green & Bavelier, 2008), such a holistic mode of learning is typically missing in artificial training programs, which separate the specific skills into blocks or subdomains to be trained in isolation. Although this mode of learning leads to rapid acquisition, it is detrimental during the retention phase and impairs transfer effects across tasks (Ahissar & Hochstein, 2004; Schmidt & Bjork, 1992).

Musical training as a model of a natural training regime seems to be a superior model for brain plasticity compared to other models available (e.g., motor or visual learning), especially due to its intricate complexity at varying levels of scale. As discussed in Moreno and Bidelman (2014), producing music involves both motor and visual engagement, thus sharing similar advantages with alternate models. They argue, however, that musical training has unique properties in terms of its breadth and permeation throughout the nervous system, which makes it difficult to find comparable activities. Perceiving and especially producing music constitutes a multimodal phenomenon that requires simultaneous processing and integrating of auditory, visual, somatosensory, and motor information, thus engaging several systems beyond the auditory domain (Christo Pantev, Lappe, Herholz, & Trainor, 2009; Wan & Schlaug, 2010; Zatorre et al., 2007). Moreover, the interplay between perceptual and action systems is particularly strong in music. The motor system, as a result of intensive musical practice, activates not only during the presentation of acoustic stimuli (Chen, Penhune, & Zatorre, 2008), but also during visual presentation of musical actions (Hasegawa et al., 2004; Haslinger et al., 2005), and manifests in tightly coupled substrates of action and perception (Bangert et al., 2006; Haslinger et al., 2005; Haueisen & Knösche, 2001; Herholz & Zatorre, 2012; Zatorre, Chen, & Penhune, 2007).

Zatorre (2005) calls music 'the food of neuroscience', and exemplifies this point by alluding to how simply 'humming a familiar tune' enforces *complex auditory pattern-processing mechanisms, attention, memory storage and retrieval, motor programming, sensory-motor integration, and so forth*, which makes music an ideal device to study wide-ranging topics in neuroscience from motor-skill learning to prediction, imagery, and even emotion, providing a window to explore the brain-behaviour connection.

Although vision requires comparable skills to those of music, and may represent an equivalent domain in terms of demands for the study of brain adaptation (e.g., perceptual acuity and pleasurable outcomes; Gardiner, Fox, Knowles, & Jeffrey, 1996), recent longitudinal training studies indicate robust advantages of music over visual arts training (Moreno et al., 2009; Moreno, Bialystok, et al., 2011; Moreno, Friesen, & Bialystok, 2011). These studies positively relate musical—but not visual—training with enhances beyond the auditory domain (speech), tapping into the visual modality and executive functions (working memory, attention, and planning; Moreno, Bialystok, et al., 2011; Moreno, Friesen, et al., 2011). As stated by Moreno and Bidelman (2014), it is possible that limitations exist in the extent to which the visual system is able to transfer skills to other cognitive abilities, perhaps because auditory skills are developed very early in life compared to visuo-motor skills (Kakebeeke, Locatell, Rousson, Caflisch, & Jenni, 2012). Empirical evidence furthermore indicates that visual experience-induced changes are moderate (Op de Beeck & Baker, 2010). Alternatively, visuo-spatial skills may need a more intensive or longer training period to significantly influence behavioural skills (Moreno and Bidelman, 2014).

In summary, studying musicians' brains constitutes an advantageous opportunity to investigate neuroplasticity, particularly in the auditory and motor domains.

1.1 Music processing in musicians and nonmusicians

A number of neuroimaging studies have indicated that brain adaptations in terms of information processing and brain structure may occur in distributed regions of the brain in accordance with the musical training history of the subject. This chapter includes a compendium of some of these findings.

Functional adaptations: Use-dependent plasticity in musicians (violin and trumpet players) has been observed in terms of enhanced brain representations for timbre-specific tones (Pantev, Roberts, Schulz, Engelien, & Ross, 2001). For instance, early onset in musical training (piano) is associated with stronger cortical auditory representations for piano as opposed to pure tones (Pantev et al., 1998). Likewise, string players exhibit more extensive contralateral somatosensory cortical representations of their left-hand fingers than nonmusicians (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Schwenkreis et al., 2007), an effect which is larger for those string players with an early onset age of practice. In support of this, musicians' motor areas seem to undergo extensive plastic changes in response to transcranial motor stimulation (TMS) compared to nonmusicians (Rosenkranz, Williamon, & Rothwell, 2007). At the brainstem level, musicians already show larger neural responses than controls (Musacchia, Sams, Skoe, & Kraus, 2007; Wong, Skoe, Russo, Dees, & Kraus, 2007). They also exhibit a mismatch negativity (MMN) in response to tones mistimed by only 20 ms (Rüsseler, Altenmüller, Nager, Kohlmetz, & Münte, 2001). Pianists show both balanced motor cortical representations, indicative of a more symmetrical motor cortex organization, and inhibitory interactions between hemispheres (Chieffo et al., 2016). This symmetry also concerns the visual domain, as musical training seems to be associated with increased functional symmetry in the interhemispheric transfer time and latency of visual responses (Patston, Kirk, Rolfe, Corballis, & Tippett, 2007). Furthermore, musical training facilitates a tighter auditory-motor coupling at the cortical level during rhythm processing (Chen, Zatorre, & Penhune, 2006; Grahn & Rowe, 2009). For instance, musicians show greater activation in frontocortical areas than controls during rhythm production (Chen, Penhune, & Zatorre, 2008). In addition, resting state findings indicate a significant increase in functional connectivity among motor, auditory, somatosensory, and visual areas (Luo et al., 2012). Further evidence shows the existence of a musicianship-specific network of frontocortical, temporal, and secondary motor areas coactive during both passive listening and key pressing on a mute keyboard (Bangert et al., 2006).

Anatomical adaptations: Grey matter volume in the anteromedial Heschl's gyri has been observed to be larger in musicians than in nonmusicians, and to correlate with musical aptitude (Schneider et al., 2002). Likewise, musicians show increased grey matter volume in auditory, motor, and visual processing areas (Gaser & Schlaug, 2003), after only fifteen months of musical training in childhood (Hyde et al., 2009). For cortical motor regions, musicians exhibit more anatomical symmetry compared to controls (Amunts et al., 1997). Further evidence indicates consistent instrument-specific anatomical differences within the right-left precentral gyrus in musicians (Bangert & Schlaug, 2006). In keeping with this, differences in the anatomy of the precentral gyrus can predict the kind of instrument played (based on different manual dominance; Bangert & Schlaug, 2006). With regard to the cerebellum, its volume is positively associated with the intensity of instrumental practice in musicians (Hutchinson, Lee, Gaab, & Schlaug, 2003). Moreover, the anterior part of the corpus callosum (CC), which connects mainly motor regions, is greater in early onset musicians (Lee, Chen, & Schlaug, 2003; Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995). Along similar lines, early onset musicians possess larger ventral premotor cortices (vPMC), which has been associated with improved auditory–motor synchronization performance (Bailey, Zatorre, & Penhune, 2014).

The development of Diffusion Tensor Imaging (DTI) has made feasible the study of white matter tracts, revealing training-related axonal differences between musicians and nonmusicians. In this regard, intermanual activity for instrument playing has an effect on fractional anisotropy (FA), a measure of the directionality of water thought to reflect fibre density, axonal diameter, and white matter myelination, within the anterior corpora callosa of musicians (Schmithorst & Wilke, 2002). Similarly, there exists an association between early musical training and FA values in musicians for the posterior corpus callosum (Steele, Bailey, Zatorre, & Penhune, 2013). Supporting this, specific instrument-training regimes may result in differences between callosal white matter organization and interhemispheric inhibition (Vollmann et al., 2014). However, findings on the effect of intensive musical training on white matter have not been consistent. For instance, two studies have reported a positive correlation between musical training and FA in the corticospinal tract (Bengtsson et al., 2005; Han et al., 2009), indicating that it increases with the length of the training if this occurs within a sensitive period of development (Bengtsson et al., 2005). This finding was inconsistent with different reports (Imfeld, Oechslin, Meyer, Loenneker, & Jancke, 2009; Schmithorst & Wilke, 2002) which have indicated the opposite trend in musicians (lower FA) in the same region. An explanation for this discrepancy could lie in the degree of heterogeneity in terms of instruments with different dexterity requirements played by the musician group in the latter study (Merrett, Peretz, & Wilson, 2013; Ullén, 2009).

In brief, brain differences between musicians and nonmusicians at the group level can be detected in auditory, motor (including primary motor and premotor cortices and cerebellum), and somatosensory areas, in addition to specific white matter bundles. Importantly, this training-induced functional reorganization may be observed through an enlarged, reduced, or shifting surface representation, which may indicate recruitment of more neurons, automatization of function, or the use of new neural processes or the setting of new representations, respectively (Habib & Besson, 2009).

1.2 Theoretical background

Because the experience of music strengthens a direct learned mapping between movement and sound, this research has an emphasis on theories that stress the embodied (i.e., grounded in perception and action; Barsalou, 2010) nature of cognition, such as embodied cognition, motor cognition, common coding theory, and (action-based) predictive coding, which relate in a general sense to the destabilizing of the mind-body antagonism. These concepts rely on the notion that sensory and cognitive systems evolved to support action, hence being dynamically coupled.

From the perspective of embodied cognition, sensory–motor evolution and cognitive evolution are not dissociable: this distinction is an arbitrary and obstructs the understanding of brain function and evolution (Barton, 2012). Both environment and body constitute the external informational structures used by the 'cognitive' system to complement internal representations (Barsalou, 2010; Gibbs, 2005). For instance, sensory-motor information can have an impact on perceptual, memory, and linguistic tasks (Barsalou, 2008; Wilson & Knoblich, 2005) and, similarly, manipulation of bodily states can affect decision making (Niedenthal, Barsalou, Winkielman, Krauth-Gruber, & Ric, 2005). Even abstract and metaphorical concepts are grounded in bodily, physical experience (Wilson, 2002).

A similar notion is that of motor cognition, which states that the motor system participates in high-level mental processes. Additionally, how we interpret others' actions is functionally coupled with our own production and perception of the same actions, a phenomenon that relies on common neural networks (Jackson & Decety, 2004). Thus, it emphasizes the processes of recognizing, anticipating, predicting and interpreting the actions of others.

Common coding theory (Prinz, 1997), inspired by the ideomotor principle of voluntary action (James, 1890; imagining an action prompts us to execute it), suggests that perceiving is a way of acting. As a consequence of performing a movement, a bidirectional association is forged between the motor pattern from which it originates, and the sensory effects that it produces (Hommel, 2004), and thus the same mental processes are shared for both observing and performing actions.

Predictive coding theory (Friston, 2002; Friston & Kiebel, 2009; Friston, 2005, 2009, 2010; Rao & Ballard, 1999) is a theory for understanding efficient coding and redundancy reduction in the nervous system. It understands the brain as an inference engine that optimizes probabilistic representations of the perceived changing sensory environment. It does so by integrating top-down expectations and bottom-up stimulus information across multiple hierarchical levels (Friston, 2005; Friston & Kiebel, 2009; Rao & Ballard, 1999). Action-oriented predictive coding emphasizes motor intentions as elicitors of the sensory results predicted by our brains (Clark, 2013). In other words, the motor system is thus actively engaged to fulfil prior expectations about the environment (Gebauer, Kringelbach, & Vuust, 2015).

Each of these theories emphasizes how humans understand all signals in terms of motor actions. In music, this becomes relevant given the patent connection between music and motor function. Johnson (1987) stresses five "action aspects" of dealing with music: (1) the sound producing actions proper, (2) the effects of these actions, (3) the possibility of imagining the sonorous unfolding as a kind of movement through time, (4) the mental simulation of this movement in terms of bodily based image schemata and (5) the movements which can be possibly induced by the sounds. Menin and Schiavo (2012) articulate this point quite effectively: "A skilled guitarist might be unable to say where to put her/his finger to perform a solo, but s/he can use the *motor knowledge* of the fingers to reconstruct the actual set of notes played, by just putting the hand on the strings. We believe that this sensory-motor process not only represents the basis of musical understanding, but it can also shed light on the notion of musical affordance, relying on a sub-cognitive, pre-linguistic, intrinsically motor form of intentionality".

1.3 Naturalistic fMRI

1.3.1 FMRI

Functional Magnetic Resonance Imaging (fMRI; Kwong et al., 1992; Ogawa et al., 1992) is among the main non-invasive techniques that enables the study of the brain in action in living humans. FMRI measures the relative amount of oxygenated hemoglobin to deoxygenated hemoglobin in the blood, which is interpreted as an indirect measure of neural activity. Animal studies have provided strong evidence in supporting this relationship between neural activity (local field potentials) and measured fMRI signal (Logothetis, Pauls, Augath, Trinath,

& Oeltermann, 2001). However, the coupling between neural activity and blood flow remains to be fully understood.

The statistical analysis of fMRI data most commonly aims to (a) localize brain areas activated by the task of interest, or (b) investigate relationships between brain areas. In the first case, the general linear model (GLM) is the most frequently used statistical approach, and is useful in comparing different tasks or events, or to map brain activity related to the performance of a task of interest. This analysis is "massive univariate", which means that a separate GLM analysis is performed at each voxel, first assuming independence between voxels but subsequently dealing with the actual dependency between voxels through means such as random field theory (RFT). In the case of studying relationships between brain areas, connectivity studies have been of increasing interest in recent years. These attempt to explore how different brain regions interact, and to which extent these interactions depend on not only the experimental tasks (Lindquist & Wager, 2014), but also during rest. During the so-called resting-state fMRI (rsfMRI), brain responses are acquired while participants are not performing any specific task. Coactivation between brain areas during rest is believed to reflect functional communication between brain regions (van den Heuvel & Pol, 2010).

Several studies have investigated the degree of reliability of fMRI findings (Specht, Willmes, Shah, & Jäncke, 2003), suggesting ways to improve fMRI reliability (Bennett & Miller, 2010), such as (a) increasing the signal-to-noise (SNR) ratio and contrast-to-noise (CNR) ratio of the acquisition, (b) reducing inter-subject differences in cognitive state, and (c) increasing the statistical power of the experiment. It is also important to remark that validity is not guaranteed by reliability. A controlled experiment yields more reliable brain responses than one with increased ecological validity, but this is trading-off validity for reliability. Thus, at the expense of decreasing reliability, by using naturalistic fMRI paradigms the researcher may increase validity (Hasson & Honey, 2012; Hasson, Malach, & Heeger, 2010).

Compared to other neuroimaging techniques, fMRI has some main advantages: (1) it is noninvasive: it does not require surgery or exposure to radiation; (2) it provides high-resolution images of the different brain tissues, allowing for high precision measurements of functional activation of subcortical areas that are almost invisible to other non-invasive techniques such as magnetoencephalography (MEG), electroencephalography (EEG) or functional near-infrared spectroscopy (fNIRS). The main disadvantage of fMRI is its lower temporal resolution (1-3 s) compared to techniques like EEG, or MEG (in the order of milliseconds), which is a result of the trade-off between spatial and temporal accuracy. Another criticism relates to hemodynamics as the indirect measure of neuronal activity on which fMRI relies. Lastly, another disadvantage of fMRI of particular relevance to the study of auditory function in the brain is the acoustic noise produced by the scanner (Formisano, Moerel, & Bonte, 2015). The most recent scanner models produce noise at around 80 dB of loudness. Measures can be taken to reduce the noise, such as noise-reducing headphones or foam around the patients' head. Finally, it is important to stress that any fMRI experiment is as good as its hypothesis, design and analysis, and to always keep in mind what research questions can be addressed by fMRI (Aue, Lavelle, & Cacioppo, 2009).

1.3.2 Naturalistic paradigm

The fMRI experimental design refers to the temporal organization structure in which participants perform cognitive or behavioural tasks during the fMRI experiment. The optimal design will depend on many factors, such as the nature of the task, the signal-to-noise ratio over time, and the specific comparisons made. These factors are directly related to the efficacy of the subsequent statistical analysis. Depending on the way stimuli are presented, traditional fMRI designs include blocked designs and event-related designs, where the main idea is to space the experimental conditions into intervals or blocks, and determine the differential activity between the two.

Controlled auditory paradigms and simple stimuli have been used traditionally in music neuroscience at the expense of ecological validity. In these highly controlled experiments the use of parameterized stimuli has been crucial in isolating the relevant dimensions from the multidimensional natural phenomena. More recently, however, neuroscientists have attempted to capture and investigate how the brain reacts to real world phenomena using naturalistic or free-behaviour tasks, towards further understanding of how the brain perceives complex, continuous multidimensional stimuli (Hasson, Nir, Levy, Fuhrmann, & Malach, 2004). Traditional and naturalistic approaches are not mutually exclusive.

Music is a rich, complex multidimensional phenomenon that unravels in time. When listening to it, all acoustic elements are processed in parallel and integrated into coherent percepts over time, producing a meaningful experience (Bregman, 1994; Johnson, 1987). This integration process considers the interactions between constituents, which are missing when processing static, simple stimuli under unimodal stimulation. Notably, ecological stimulation generates widespread activity beyond the sensory domain, such as motor-related regions, which are absent under high controlled paradigms (Bartels & Zeki, 2004a; Hasson et al., 2004). Thus, a transition to mapping brain activity using naturalistic stimuli has been fostered by the recognition that the natural world bears little resemblance to a highly controlled experimental setting, and that simple, static, unimodal stimuli cannot capture the richness of dynamic, natural phenomena (Maguire, 2012).

The dynamic quality of music is often overlooked in highly controlled lab settings. However, our adaptive brains evolved in a complex auditory scene environment, assimilating complex tones, segregating and reacting to them dynamically. To access specific aspects of the music listening experiencing it is crucial to examine how this experience unfolds over time in naturalistic conditions. Furthermore, by using a naturalistic approach to studying the brain there is no need to rely on participants' ability to self-report, which may further constrain the very brain processes under investigation.

Investigating music perception in increased true-to-life environments is not an easy undertaking, and comes at the cost of analysis complexity. With the recent developments in the field of Music Information Retrieval (MIR), new techniques allow the extraction of meaningful acoustic features from the musical stimuli facilitating the use of natural stimuli to investigate how the brain processes music. Similar computational approaches have been successfully used during naturalistic movie-viewing experiments, evidencing the ecological importance of such approaches (Hasson, Furman, Clark, Dudai, & Davachi, 2008; Hasson et al., 2004; Hutcherson et al., 2005). Consequently, naturalistic paradigms are becoming more technically feasible for studying human brain functions. In addition, for the analysis of naturalistic fMRI data, participants' behavioural responses can be subsequently recorded to retrospectively analyze their data, such as with a passive listening fMRI scanning. Alternatively, patterns in brain activity can be found by employing computational feature extraction (Alluri et al., 2012) or mathematical algorithms such as multi-voxel pattern analysis (MVPA; Norman, Polyn, Detre, & Haxby, 2006), Independent Component Analysis (ICA; McKeown & Sejnowski, 1998), or complex network analysis (Bullmore & Sporns, 2009).

The increasing use of naturalistic paradigms in neuroscience demonstrates that true-to-life environments can yield reliable results, with increased ecological validity.

2 RESEARCH AIMS

While traditional mass-univariate fMRI analyses target functional segregation (also called differentiation), i.e., the relative independence of brain regions for some aspect of a function, more recent approaches investigate integration, which refers to the deviation from independence in large groups of neural elements (Boccaletti, Latora, Moreno, Chavez, & Hwang, 2006). Because the cortical substrate underlying a single function may require multiple other contributions which are mediated by functional integration among them, *functional segregation is only meaningful in the context of functional integration and vice versa*, as put by Friston (2011).

In music neuroscience, connectivity studies have provided new insights into the relationship between integrative brain function and musical training. By exploring interactions and internal dependencies within the functional brain structure, such studies provide a complementary knowledge to that obtained using segregation measures. However, often the materials and settings used are not naturalistic. The main motivation of this research work is thus to investigate integrative brain function in response to naturalistic, online listening of complex music in listeners with and without professional musical training using fMRI, while trying to understand whether differential brain activity may be accounted for by brain adaptations, as a consequence of intensive musical training. Special emphasis is laid on the sensorimotor aspect of music listening. In the naturalistic paradigm used, participants have no specific task but to attentively listen to continuous, real-world pieces of music of different genres (see Figure 1 for a schematic view of the paradigm). Such a laboratory environment relies on both complex and realistic auditory material and setting, resembling more closely real-world music listening contexts. This has the potential to increase the validity of the findings over those of controlled approaches, which is critical to modelling how the brain understands the world.

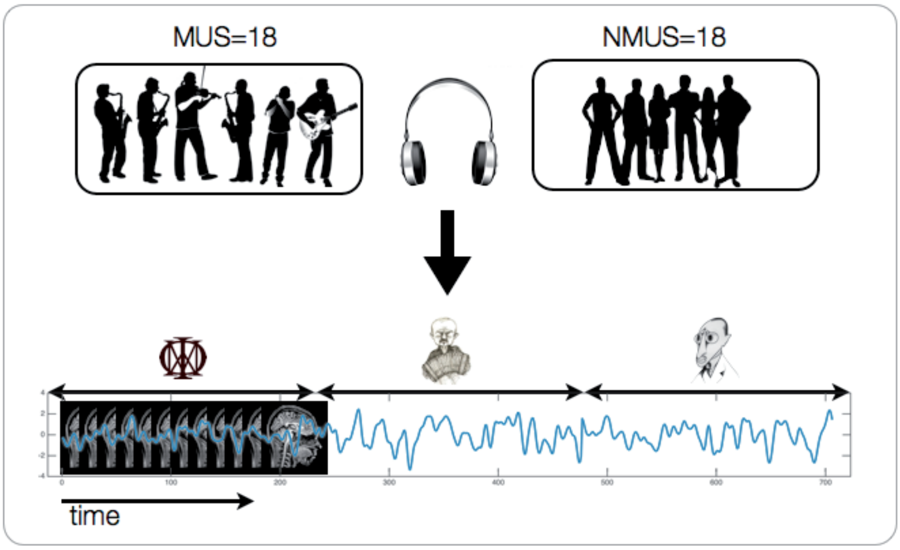

FIGURE 1 Schematic view of the naturalistic paradigm used.

Four studies are included in this thesis:

> *(I) Burunat, I., Toiviainen, P., Alluri, V., Bogert, B., Ristaniemi, T., Sams, M., & Brattico, E. (2016). The reliability of continuous brain responses during naturalistic listening to music. NeuroImage, 124, 224–231. doi:10.1016/j.neuroimage.2015.09.005.*

First, a replication study (I) was conducted to test the reliability of a previous naturalistic approach by Alluri et al. (2012), which uncovered the neural correlates of timbral, tonal, and rhythmic feature processing during music listening, wherein brain and acoustic signal were correlated. The successful replication supported the study of brain processes using naturalistic stimulation, increasing the ecological validity of the findings. Using the same naturalistic fMRI dataset, a series of four studies followed, all of which dealt with differences in integrative brain function during music listening between musicians and nonmusicians.

> *(II) Burunat, I., Brattico, E., Puoliväli, T., Ristaniemi, T., Sams, M., & Toiviainen, P. (2015). Action in Perception: Prominent Visuo-Motor Functional Symmetry in Musicians during Music Listening. PLOS ONE, 10(9), e0138238. doi:10.1371/journal.pone.0138238*

This hypothesis-driven study (II) investigated connectivity by computing whole-brain interhemispheric homotopic functional connectivity, which provides a measure of the functional symmetry of the brain responses. The aim was to study group differences in the extent and location of the functional symmetry as a function of musical training. Differences were expected in somatosensory and motor control areas in agreement with the specific motor demands of musicianship, which require a higher level of dexterity compared to nonmusicians. Differences between keyboard and string players were also investigated.

(III) Burunat, I., Brattico, E., Hartmann, M., Vuust, P., Särkämö, T., & Toiviainen, P (under review). Music training predicts cerebello-hippocampal coupling during music listening.

This hypothesis-driven study (III) investigated differences in cerebello-hippocampal (CER-HIPP) connectivity between listeners with and without musical training. These were hypothesized based on between-group differences in predictive listening abilities. The hypothesis was based upon the evidence that coupling between cerebellum and hippocampus occurs during accurate spatio-temporal prediction of movements (Onuki, Van Someren, De Zeeuw, & Van der Werf, 2015). Thus, in the context of music listening, differences in CER-HIPP connectivity may result from differences in predictive listening accuracy.

(IV) Burunat, I., Tsatsishvili, V., Brattico, E., & Toiviainen, P. (under review). Coupling of action-perception brain networks during rhythm processing: Evidence from region-of-interest-based independent component analysis.

This data-driven study (IV) investigated differences in the processing of pulse clarity between musicians and nonmusicians during music listening using a region-of-interest (ROI)-based independent component analysis (ICA) approach, with an additional comparison of results using the GLM approach. In (IV) group differences in pulse clarity processing were hypothesized based on musicians' improved models of beat induction (Aschersleben, 2002; Drake, Penel, & Bigand, 2000; Hove, Keller, & Krumhansl, 2007; Krause, Pollok, & Schnitzler, 2010; Repp, 2010; Repp & Doggett, 2007). Additionally, functional networks sustaining pulse clarity processing were expected to overlap with cortical-subcortical auditory-motor networks observed in previous studies on rhythm processing.

Various statistical univariate and multivariate analysis methods and numerical tools were used in this research, including GLMs, ICA, psychophysiological interactions (PPI), kernel density estimation (KDE), unconstrained nonlinear optimization, Dice coefficient, Principal Component Analysis (PCA), and permutation-based nonparametric procedures. The implementation of these techniques relied on customized scripts developed by the authors in the Matlab environment and thus standard neuroimaging analysis software packages available in the market were not employed for the statistical inference of the present findings.

The studies included in this thesis combine both theory- and data-driven approaches. As put by Makeig et al. (1998), "[…] These two approaches are complementary and mirror the exploratory and confirmatory aspects of scientific investigation. Imaging studies driven by hypotheses derived from cognitive psychology and related disciplines can at best support or refute currently formulated psychological models. Counterintuitive or unanticipated time courses of activation of localized brain areas are less likely to be discovered with such analysis methods”. Thus, the interaction of the two approaches would drive the most fruitful scientific investigation, especially when attempting to understand complex phenomena.

3 STUDY SUMMARIES

The papers included in this thesis used a common fMRI dataset. It comprised brain responses from listeners (18 professional musicians and 18 controls) acquired while they listened to natural music. The criteria for musicianship was for participants to have more than five years of music training, have finished a music degree in a music academy, report themselves as musicians, and having worked professionally as a performer. In the scanner, participants' only task was to attentively listen to the music delivered via high-quality MR-compatible insert earphones while keeping their eyes open. The three musical pieces used in the experiment were presented in a counterbalanced order. The pieces were (a) Stream of Consciousness by Dream Theater; (b) Adios Nonino by Astor Piazzolla; and (c) Rite of Spring (comprising the first three episodes from Part I: Introduction, Augurs of Spring, and Ritual of Abduction) by Igor Stravinsky. These are a progressive rock/metal piece, an Argentinian New Tango, and an iconic 20th century classical work, respectively, thus covering distinct musical genres and styles. All three selected pieces are instrumental and each of them has a duration of about 8 minutes. For Study I, only the brain responses to the Piazzolla stimulus were used, given the replication nature of the study, whereas for studies II, III, and IV, brain responses to the three stimuli were concatenated (this made a total of ~24 minutes worth of data). The purpose of such concatenation was to combine brain responses to stimuli representing a broad range of musical styles to cancel out confounding effects that the specific type music may exert on the results, rendering findings more generalizable (see Figure 1).

3.1 Study I: Reliability of the naturalistic listening paradigm

Motivation: Scientific findings and paradigms are of little use unless their validity is widely accepted: a stage in scientific research reached by demonstrating that the methods in question produce useful results. The purpose of this study was to aim at replicating previous results on naturalistic musical feature processing in the brain to test the robustness of the paradigm used.

The novel naturalistic fMRI paradigm in question was employed by Alluri et al. (2012; in the following, "the original study"). It allowed them to predict the temporal evolution of brain activations to musical features at a voxel level. Low-level (timbral) and high-level (tonal and rhythmical) musical features were observed to elicit large-scale neural responses in cognitive, motor and limbic brain networks. Using an identical methodological approach, the same musical stimulus (*Adios Nonino* by Astor Piazzolla) and a similar group of participants, Study I aimed to quantify the replicability of previous findings. Figure 2 illustrates the experimental design of Study I.

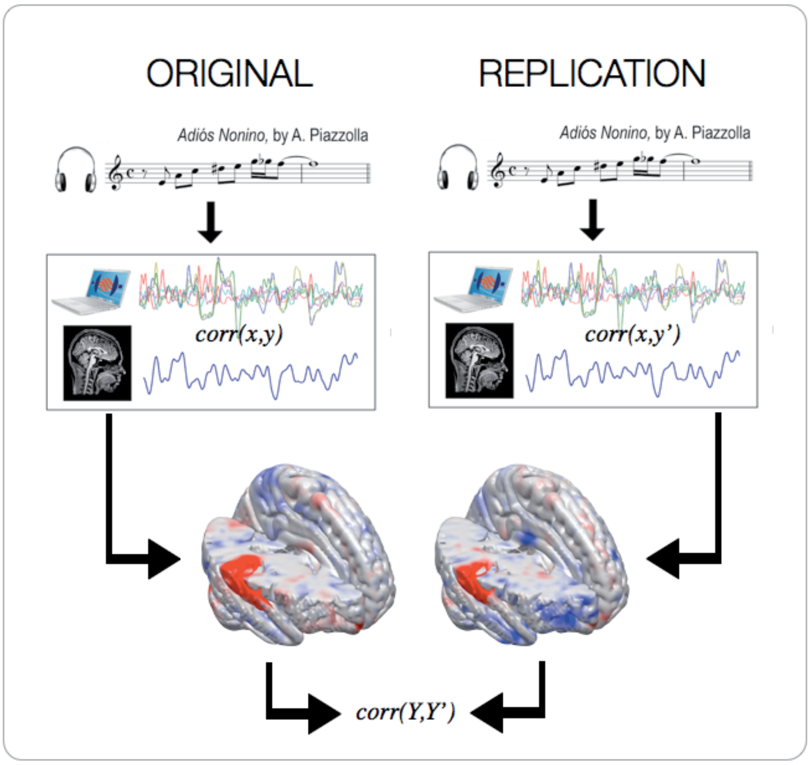

FIGURE 2 Experimental design of Study I (color online).

Methods: Participants' fMRI responses to the musical stimulus were correlated voxelwise against the six time series of perceptually validated musical features used in the original study, which had been computationally extracted from the musical stimulus using MIR Toolbox (Lartillot & Toiviainen, 2007), and perceptually validated. These musical features were Fullness, Brightness, Timbral Complexity, Activity, Pulse Clarity, and Key Clarity (see Alluri et al., 2012 & Alluri & Toiviainen, 2010 for a detailed description on the procedures to obtain these musical percepts). The similarity of results between the original study and our present study was assessed by two approaches: (a) correlating the respective activation maps (via the intraclass correlation coefficient, ICC); and (b) computing the overlap of active voxels between datasets at variable levels of ranked significance. The approach in (a) measured the similarity of the whole extent of spatial activations by correlating the resulting continuous spatial maps from the original and replicated experiments. The statistical significance of the ICCs was estimated via a non-parametric approach based on permutation tests (see 4.1.2). The approach in (b) entailed comparing a proportion of the top significant voxels from each pair of compared maps by computing the Dice overlap coefficient (Dice, 1945) between them as shown in (1),

$$s_{xy} = \frac{|X \bigcap Y|}{|X| + |Y|}, \tag{1}$$

where X and Y denote the proportion of the most significant voxel in the original and replication studies, respectively, and s_{xy} yields the ratio of intersected voxels to the number of voxels in the evaluated set, normalized to the range $[0,1]$. The significance of the resulting overlaps was assessed by generating a H_o distribution of overlaps by means of permutation tests for each of the proportions of brain volume compared (see 4.1.3).

Both (a) and (b) reliability measures are intraclass measures, which tackle similarities between group-level measurements in two different participant pools. Additionally, the way these measures are implemented avoids relying on a predefined significance threshold (e.g., a cut-off Z-value) because the maximal significance level obtained for each experiment can differ due to existing SNR differences between scanners and variances related to the different group of participants.

Results: The approach in (a) revealed significantly similar spatial activations for the pair of maps related to the timbral features (Fullness, Timbral Complexity, and Activity), while for the tonal (Key Clarity) and rhythmical (Pulse Clarity) features it did not reach significance at the conventional alpha levels (see Figure 3). The approach in (b) allowed the identification of brain regions with the most significant overlaps, i.e., the best replicable areas for each of the musical features. The focus of highest reliability across all maps was observed within the auditory cortices, except in the case of Key Clarity, for which the focus of reliability was scattered. Overall, timbral features were more successfully replicated than tonal and rhythmical ones, which may suggest more universal processing mechanisms for the low-level musical features as compared to higher-level features. These may be more dependent on more cognitive, top-down mechanisms associated with larger participant-dependent variability in the hemodynamic responses, which would reduce replicability.

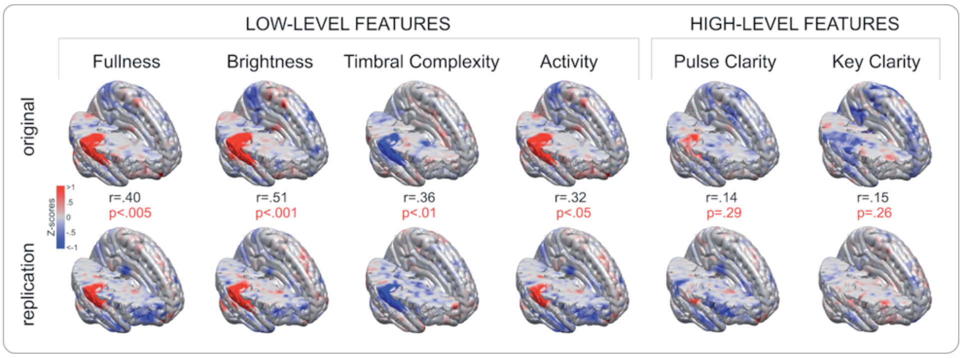

FIGURE 3 Results of the ICC measure. The spatial maps represent the brain correlates of each musical feature from the original and replication experiments. The ICC and its significance value are indicated for each pair of maps.

3.2 Study II: Functional symmetry and musical expertise

Motivation: Study II was largely motivated by previous findings relating to an enlarged anterior corpus callosum (CC) in musicians (Lee et al., 2003; Schlaug et al., 1995) and on the enhanced somatosensory left-hand finger representation in string players (Elbert et al., 1995). As callosal volume has been found to be a predictor of interhemispheric transfer capacity (Jaencke & Steinmetz, 1994; Witelson, 1985), and a positive relationship seems to exist between callosal area and the number of fibres crossing through the CC (Aboitiz, Scheibel, Fisher, & Zaidel, 1992), differences in callosal size may relate to differences in interhemispheric functional connectivity. However, it is important to note that there is no scientific consensus on the relationship between callosal size and interhemispheric transfer capacity (Banich & Shenker, 1994; Pizoli, Shah, Snyder, Shimony, & Limbrick, 2011; Reilly et al., 2013; Tyszka, Kennedy, Adolphs, & Paul, 2011; Uddin et al., 2008; Wang, Dai, Gong, Zhou, & He, 2014). Furthermore, studies on interhemispheric communication in musicians and nonmusicians are limited. Thus, we aimed to investigate functional symmetry differences as a function of musical training during music perception (naturalistic music listening). Here functional symmetry denotes the degree of temporal synchrony between brain responses occurring at equidistant areas along the midline of the brain (also called “voxel-mirrored homotopic connectivity”; Zuo et al., 2010). We hypothesized that musicians would exhibit more prominent functional symmetry compared to nonmusicians, particularly within the motor system. Similarly, we hypothesized keyboard players (N=8) to show increased functional symmetry compared to string players (N=7), based on string players’ cortical representational asymmetry (Elbert et al., 1995; Schwenkreis et al., 2007). Additionally, morphometric analyses of participants’ CC were performed. Figure 4 illustrates the experimental design of Study II.

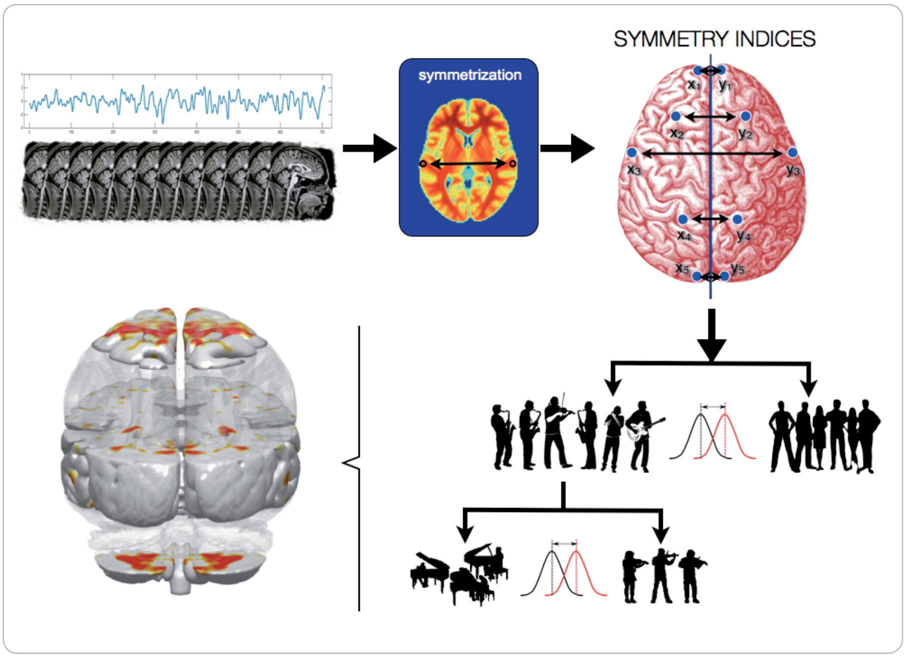

FIGURE 4 Experimental design of Study II.

Methods: Because the brain is not symmetrical, homotopic voxels are not necessarily anatomically analogous. In order to make the claim for homotopic symmetry stronger, participants' brains were transformed using a spatial mapping derived from an optimization approach, so that

$$\tilde{\mathbf{a}} = \arg\min_{a} \frac{1}{V(B_L)} \int_{B_L} \left[b(f_a(r(\mathbf{x}))) - b(\mathbf{x})\right]^2 d\mathbf{x}, \tag{2}$$

where $\tilde{\mathbf{a}}$ denotes the optimal parameters for f_a, a transformation which maps the right hemispheric intensity values $b(r(\mathbf{x}))$ onto their homotopic ones $b(\mathbf{x})$, with $\mathbf{x}$ representing a 3D location (x,y,z) in the left hemisphere ($\mathbf{x} \in B_L$), so that the cost function yields the minimum error.

To obtain functional symmetry maps, each participant's fMRI brain responses to music were correlated at every voxel with their hemispheric counterparts. Fisher Z-transformed spatial maps were subjected to t-tests between groups (directional unpaired two-sample t-tests; *alpha* = 0.01, one-tailed), to observe the brain areas where each of the groups showed significantly greater symmetry over the other. The resulting differential maps underwent multiple comparisons correction using a cluster-wise significance approach (see 4.1.4). Pairs of homotopic voxels for which symmetry indices did not reach significance at the group level (Fisher's combined probability test; Fisher, 1925, $p < 0.0005$, right-tailed) were discarded from the final maps.

Morphometric analyses of the CC were performed using the FreeSurfer[1] image analysis suite. T-tests were performed to investigate a potential relationship between participants' callosal sizes and their group membership.

Results: Morphometric results revealed that only musicians' posterior callosa were significantly larger compared to those of nonmusicians (see Figure 5). This result is in disagreement with previous findings (Lee et al., 2003; Schlaug et al., 1995), which reported to find a larger anterior, and not posterior, callosum for musicians. Additionally, no relationship was found between callosal volumes and functional symmetry.

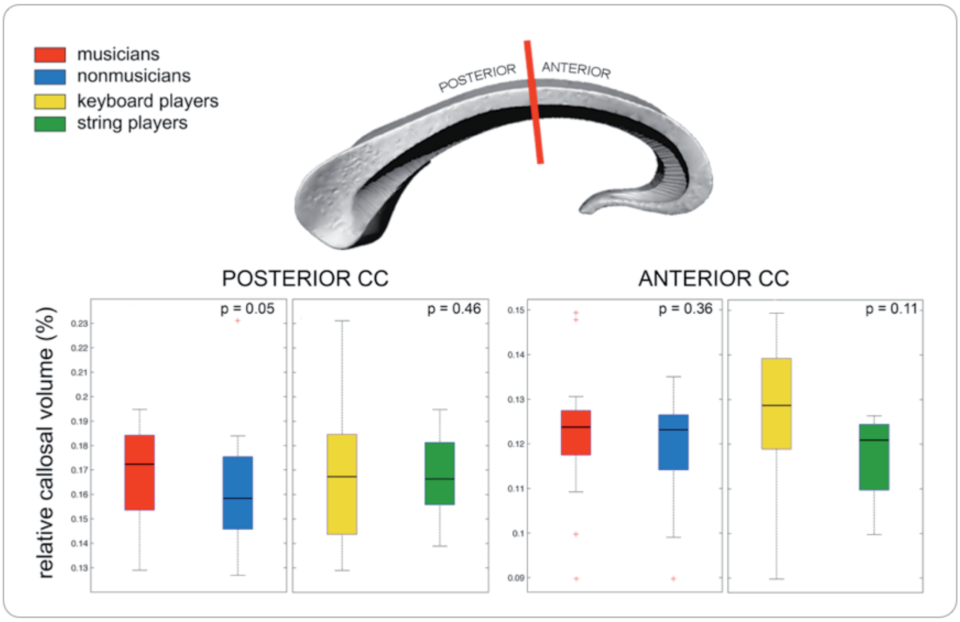

FIGURE 5 Results of the morphological analyses of the corpus callosum.

As for the functional connectivity analyses, musicians showed stronger functional symmetry than nonmusicians, but not vice versa. Musicians' prominent functional symmetry was located within somatomotor regions, and to a lesser extent within visual, temporal and prefrontal cortices. Keyboardists' increased symmetrical responses, compared to string players, were most extensively observed in visual processing areas, followed by motor areas. In addition, string players exhibited more functional symmetry than keyboardists in one small area within the middle and superior frontal gyri (see Figure 6).

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[1] Available online at https://surfer.nmr.mgh.harvard.edu

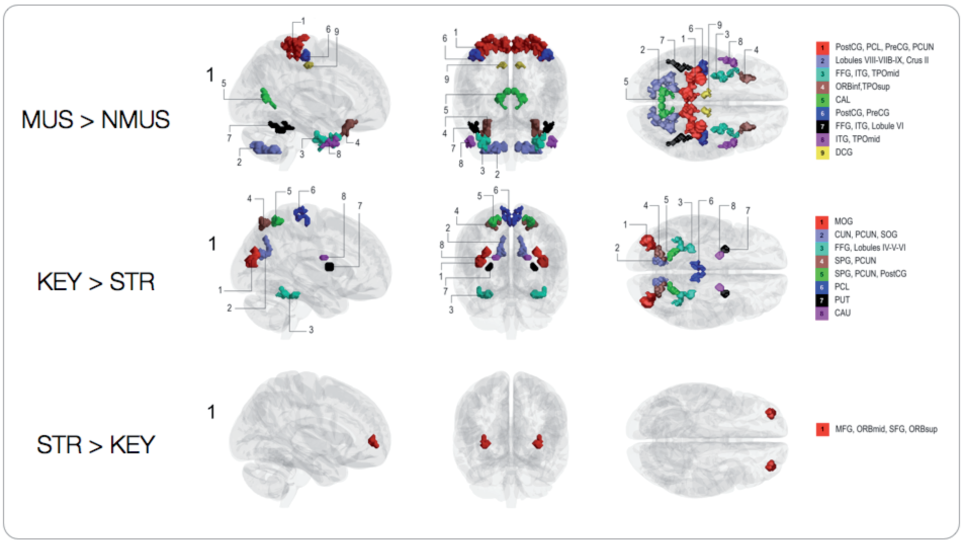

FIGURE 6 Symmetry profiles for the group comparisons. Abbreviations: MUS: musicians; NMUS: nonmusicians; KEY: keyboard players; STR: string players; PostCG: postcentral gyrus; PCL: paracentral lobule; PreCG: precentral gyrus; PCUN: Precuneus; FFG: fusiform gyrus; ITG: inferior temporal gyrus; TPOmid: temporal pole (middle temporal gyrus); ORBinf: orbitofrontal cortex (inferior frontal gyrus); TPOsup: temporal pole (superior temporal gyrus); CAL: calcarine fissure and surrounding cortex; DCG: median cingulate and paracingulate gyrus; MOG: middle occipital gyrus; CUN: cuneus; PCUN: precuneus; SOG: superior occipital gyrus; FFG: fusiform gyrus; SPG: superior parietal gyrus; PostCG: postcentral gyrus; PCL: paracentral lobule; PUT: putamen; CAU: caudate nucleus; MFG: middle frontal gyrus; ORBmid: orbitofrontal cortex (middle frontal gyrus); SFG: superior frontal gyrus; ORBsup: orbitofrontal cortex (superior frontal gyrus).

Because the increased symmetry in musicians was mainly observed within the somatosensory and motor systems, findings are consistent with the specific motor demands of musicianship (Hyde et al., 2009), requiring a higher degree of dexterity in musicians compared to nonmusicians. The higher symmetry of keyboardists in mainly visual areas can be understood as resulting from the demands of acquiring visual information during score reading for both hands, while simultaneously monitoring their synchronized movements.

3.3 Study III: Cerebello-hippocampal connectivity

Motivation: Musical experience is crucially linked to prediction (Gebauer et al., 2015; Huron, 2006; Maidhof, Vavatzanidis, Prinz, Rieger, & Koelsch, 2010; Meyer, 1956; Narmour, 1990; Rohrmeier & Koelsch, 2012; Schenker, 1935; Schoenberg, 1978; Vuust, Ostergaard, Pallesen, Bailey, & Roepstorff, 2009), and musicians exhibit stronger brain responses to expectation violations in musical contexts compared to controls (James, Britz, Vuilleumier, Hauert, & Michel, 2008; Koelsch, Jentschke, Sammler, & Mietchen, 2007; Koelsch, Schmidt, & Kansok, 2002; Oechslin, Van De Ville, Lazeyras, Hauert, & James, 2013; Vuust et al., 2011; Vuust, Brattico, Seppänen, Näätänen, & Tervaniemi, 2012). A recent study by Onuki et al. (2015) found connectivity between posterior cerebellum and left hippocampus when participants were predicting motor sequences following visual cues. This study investigates whether this network exists in the context of music listening in musically trained and untrained individuals, and in particular how the degree of CER-HIPP coupling depends on the predictability of the music. A stronger CER-HIPP coupling in musicians compared to nonmusicians could indicate improved predictive listening accuracy on the basis of action simulation mechanisms (i.e., during listening, musicians may be mentally simulating sound-producing actions). This simulation would be facilitated via strengthened coupling between produced and heard sounds through life-long instrument practice, which in turn would aid in generating predictions about the future course of the perceived sounds (Pezzulo, Candidi, Dindo, & Barca, 2013; Sebanz & Knoblich, 2009; Wilson & Knoblich, 2005). Figure 7 illustrates the experimental design of Study III.

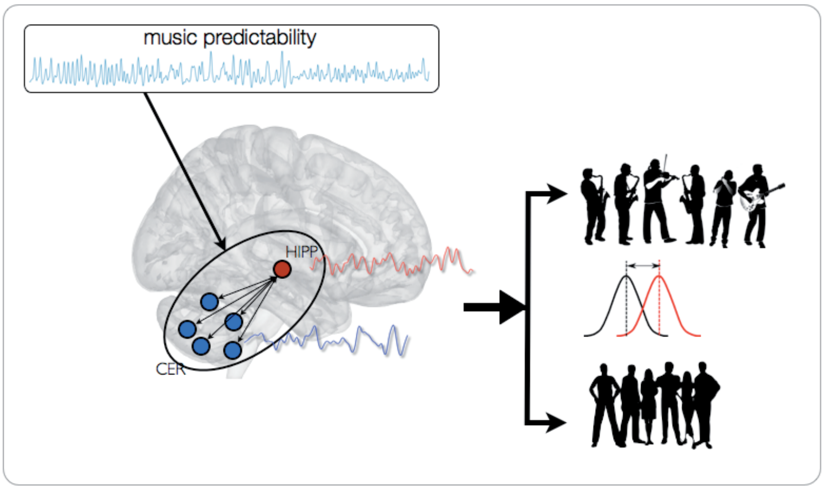

FIGURE 7 Experimental design of study III.

Methods: Functional connectivity was measured between four seed regions within the bilateral hippocampus (along an anterior-posterior gradient according to the uncus) and the cerebellum. The seeds represented the averaged hemodynamic activity within each bilateral hippocampal division (see Figure 8).

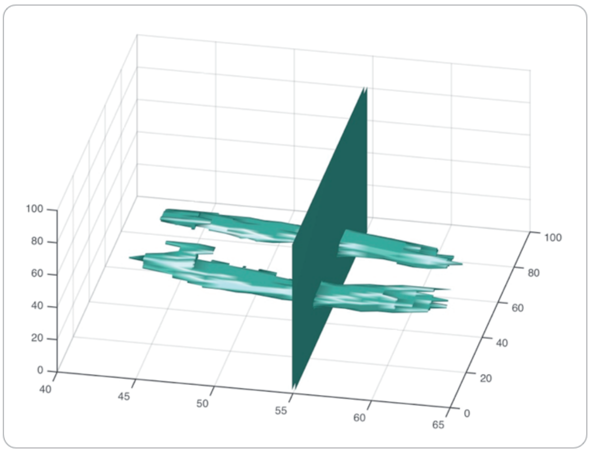

FIGURE 8 Hippocampal division used for the PPI analyses.

In addition, an information theory-based measure of the perceptual predictability of the music was obtained by means of a perceptual experiment to conduct second-order functional connectivity analyses. This measure described for each group the moments with high information content[2] in the music, found at segment boundaries, after which upcoming auditory events were hardest to predict (cf. Cohen, Adams, & Heeringa, 2006; Narmour, 1990; Pearce, Ruiz, Kapasi, Wiggins, & Bhattacharya, 2010; Pearce & Wiggins, 2006; Saffran, Johnson, Aslin, & Newport, 1999). Thus, this variable made it feasible to conduct PPI analyses to evaluate whether CER-HIPP connectivity was mediated by the degree of predictability of the music. PPI analyses are task-dependent connectivity analyses, which allow the study of how brain regions interact in a task-dependent manner (Friston et al., 1997). PPI measures how connectivity is affected by an external (psychological) variable, i.e., how the presence or absence of it modulates the connectivity. The statistical model for PPI is the multiple linear regression

$$\mathbf{x}_i = \mathbf{x}_k \times \mathbf{g}_p \cdot \beta_i + [\mathbf{x}_k \mathbf{g}_p \mathbf{G}] \cdot \beta_G + e_i, \qquad (3)$$

where $\mathbf{x}_k$ denotes the physiological responses (the fMRI signal at a seed region, here the HIPP seed), $\mathbf{g}_p$ denotes the psychological variable (here the predictability of the music) convolved with a canonical hemodynamic response function (HRF), $\mathbf{x}_k \times \mathbf{g}_p$ represents thus the psychophysiological interaction term between the HIPP seed activity and the predictability of the music (see Figure 9), $\mathbf{x}_i$ denotes the brain responses at each voxel within the cerebellum, β_i denotes

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[2] The information content of an event is inversely proportional to its probability, and thus it denotes its unexpectedness (Mackay, 2003).

the beta parameter estimates corresponding to the PPI term; β_G is a matrix of the beta estimates corresponding to $\mathbf{x}_k$ and $\mathbf{g}_p$, as confounding variables, and other potential covariates of no interest ($\mathbf{G}$); and $\mathbf{e}_i$ is the error term. Thus, the PPI term represents the explanatory variable in a multiple linear regression, and the inclusion of $\mathbf{x}_k$ and $\mathbf{g}_p$ as nuisance regressors guarantees any confounding effect induced by their variability alone to be ruled out. Cerebellar areas in which activity is best predicted by the PPI term indicate areas with strongest correlation with the hippocampal seed as a function of the predictability of the music. The Z-transformed PPI beta parameter estimates were compared between groups by means of t-tests (*alpha* = 0.01, one-tailed), and the resulting maps were cluster-wise thresholded (see 4.1.4). Additional correlation analyses tested a potential relationship between the duration of the musical training and the predictability-driven functional connectivity.

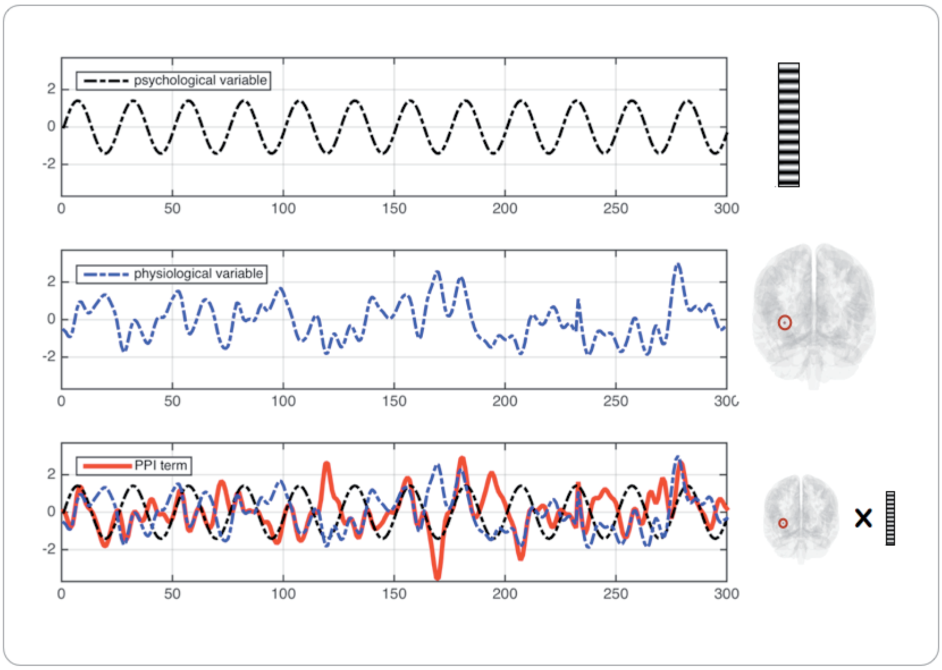

FIGURE 9 Example of creation of a PPI term.

Results: Overall, statistical analyses revealed that musicians exhibited increased and more extensive CER-HIPP coupling than nonmusicians during segments of the music with low information content. In other words, musicians exhibited a greater effect of music predictability on the CER-HIPP network than nonmusicians. Specifically, this increased predictability-driven connectivity was observed between the posterior CER and all HIPP seeds except for the right posterior HIPP seed (see Figure 10). The fact that the areas involved represent cognitive-related CER regions in the posterior lobe, implicated in higher-level tasks

(Stoodley & Schmahmann, 2009), is in keeping with the notion that a cognitive aspect—rather than a motor one—underlies the predictive component of the CER-HIPP coupling. Moreover, the musicians' network overlapped with findings by Onuki et al. (2015), whose network comprised posterior CER and left HIPP. On the other side, nonmusicians' predictability-driven connectivity was observed between right posterior HIPP and CER lobules IV-V (anterior lobe) and VI (posterior lobe). Because the anterior lobe has not been associated in previous prediction tasks (Keren-Happuch, Chen, Ho, & Desmond, 2014; Stoodly, Valera, & Schmahmann, 2012; Strick, Dum, & Fiez, 2009), nonmusicians' findings cannot be as clearly accounted for by previous work on cerebellar predictive functions. Additionally, there was no overlap between nonmusicians' results and those by Onuki et al. (2015).

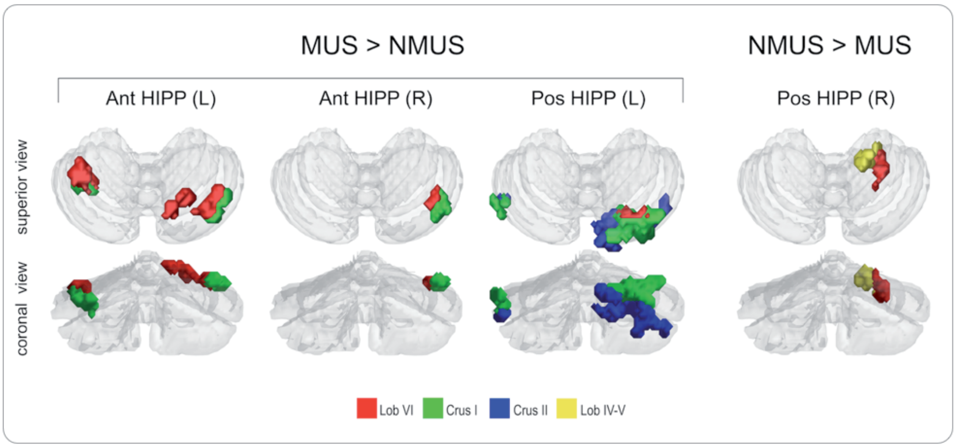

FIGURE 10 Results of the PPI analyses. Highlighted regions exhibited increased predictability-driven CER-HIPP functional connectivity in musicians compared to nonmusicians for three of the seeds, and in nonmusicians compared to musicians for one of them. Abbreviations: Ant: anterior; Pos: posterior; HIPP: hippocampus; L: left; R: right; MUS: musicians; NMUS: nonmusicians.

The stronger CER-HIPP coupling could hence be a marker of more accurate predictive listening in musicians than in nonmusicians on the grounds of spatio-temporal predictive mechanisms such as action simulation, allowing participants to anticipate upcoming musical events. Additionally, musicians' increased predictability-driven connectivity was positively correlated with the length of their musical training, supporting the role of musical training in driving the connectivity.

3.4 Study IV: Pulse clarity processing

Motivation: Spontaneously moving to the beat may be one of the most, if not the most, enthralling effects of music (Repp & Su, 2013; Zentner & Eerola, 2010). Attempting to understand the brain processes sustaining rhythm perception represents a major challenge in cognitive science (Clarke, 1989; Gabrielsson, 1987; Large & Palmer, 2002; Palmer, 1989; Repp, 1990). Neuroimaging evidence indicates that the motor system (premotor cortex, supplementary motor area, basal ganglia, and cerebellum) activates in response to rhythm perception, despite the absence of manifest movement (Chen et al., 2008; Geiser, Notter, & Gabrieli, 2012; Grahn & Brett, 2007; Schubotz, Friederici, & Von Cramon, 2000). Recently, studies on brain connectivity have disentangled interactions between activity in the auditory and motor systems during rhythm processing (Chen et al., 2006; Grahn, 2009; Grahn & Rowe, 2009; Kung, Chen, Zatorre, & Penhune, 2013; Zatorre, Chen, & Penhune, 2007c), and also revealed musical training as an enhancer of such auditory-motor connectivity at the cortical level (Chen et al., 2008, 2006; Grahn & Rowe, 2009). However, rhythm processing and the impact of musical training thereon need to be addressed in the context of complex, real-life music, and explored by using methodological tools beyond the GLM, to allow for the study of brain activity as modelled by the researcher. This study employed ICA to decompose the brain activity into spatially independent but functionally connected brain networks. Because ICA is a blind source separation technique, and therefore data-driven, it requires no prior model of the temporal course of the hemodynamic activations, allowing for a more flexible study of brain behaviour and a complementary technique more constrained approaches such as GLM. In addition, ICA is becoming increasingly popular for the analysis of fMRI signals acquired during the processing of complex stimuli with reliable results (Bartels & Zeki, 2005; Bartels & Zeki, 2004b; Malinen, Hlushchuk, & Hari, 2007; Wolf, Dziobek, & Heekeren, 2010).

The aim of Study IV was to investigate an aspect of rhythm processing, namely clarity of the pulse, during naturalistic music listening. The hypotheses proposed were that (a) group differences would exist in pulse clarity processing, as suggested by musicians' improved ability to internally keep the beat, as evident through tapping tasks (Aschersleben, 2002; Drake et al., 2000; Hove et al., 2007; Krause, Pollok, et al., 2010; Repp, 2010; Repp & Doggett, 2007), and (b) pulse clarity processing would be sustained by a cortical-subcortical auditory-motor brain network, consistent with previous neuroimaging studies. Figure 11 illustrates the experimental design of Study IV.

Methods: Prior to ICA analysis, the dimensionality of participants' brain responses was first reduced at both the participant and group levels using PCA. The dimensionally reduced data were then decomposed into independent components (ICs) by means of ICA. The ICA model is defined as follows:

$$\mathbf{X} = A\mathbf{S}. \tag{4}$$

Here, $\mathbf{X}$ represents the time-by-voxel data matrix of observable brain signals, $\mathbf{S}$ denotes an unknown time-by-voxel data matrix of source signals that are maximally independent, and $\boldsymbol{A}$ is an unknown mixing matrix. ICA estimates both $\boldsymbol{A}$ and $\mathbf{S}$ by using only observations in the linear mixture $\mathbf{X}$. The independence assumption implies that the activations do not overlap in space (Lindquist, 2008; see 4.2 for an extended description). Only brain responses from a ROI related to rhythm processing observed in previous research were included in the analyses. This ROI comprised auditory, somatomotor, basal ganglia, and cerebellar areas. ICA was performed via ICASSO, a robust analysis tool that runs the IC algorithm iteratively and clusters similar IC estimates (Himberg & Hyvärinen, 2003; Himberg, Hyvärinen, & Esposito, 2004).

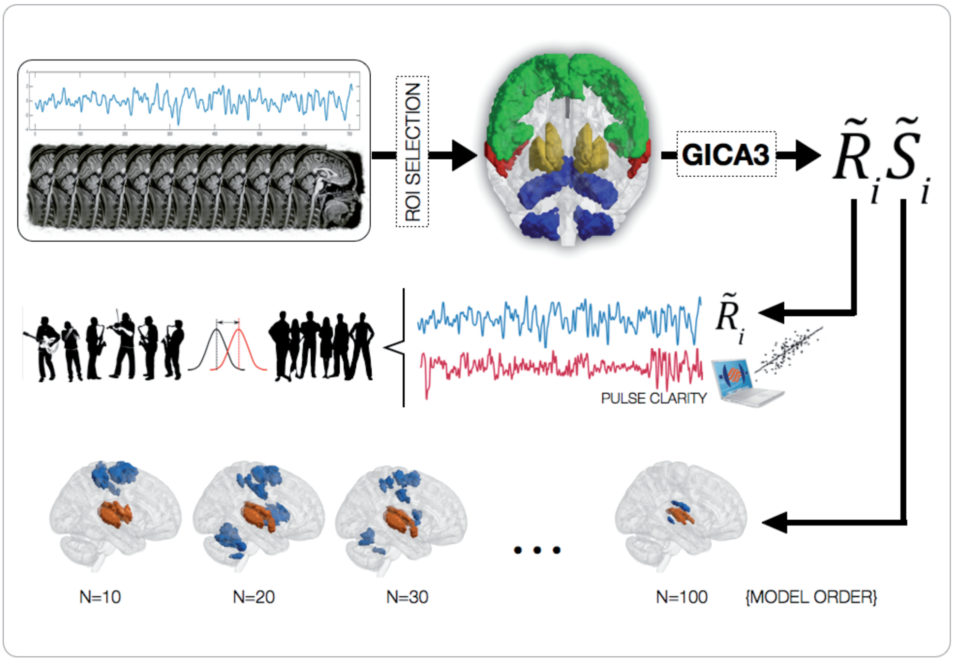

FIGURE 11 Experimental design of study IV (color online).

Because a model order (i.e., number of sources) needs to be assumed prior to source separation, a selection of ten different model orders (ranging from 10 to 100 in steps of 10) was chosen. From each model order, the IC that most significantly correlated with a measure of the pulse clarity of the music was identified and compared between groups. MIR Toolbox (Lartillot & Toiviainen, 2007) was used to obtain the pulse clarity measure, which underwent a similar preprocessing as applied to the fMRI data and further HRF convolution to conform with the hemodynamic delay. This comparison was achieved by reconstructing subject-specific IC temporal courses using the GICA3 algorithm (Erhardt et al., 2011). For all pulse clarity-driven ICs, ICASSO stability indices (I_q; Himberg et al., 2004) were retrieved. The I_q measures the compactness and isolation of a cluster of similar ICs extracted in each ICASSO run, and ensures that the ICs of interest have high reliably, and thus are stable and robust (see Figure 12). Lastly, the associated functional networks for each pulse clarity-driven IC were examined at the participant pool level, for which a one-sample Wilcoxon signed rank test (*alpha* = 0.001, cluster-wise corrected, FWE = 0.05) was used (see 4.1.4). In addition, GLM analyses were conducted for comparison purposes by correlating the ROI brain responses against the measure of pulse clarity for both musicians and nonmusicians. Figure 13 summarizes the ICA methodological pipeline.

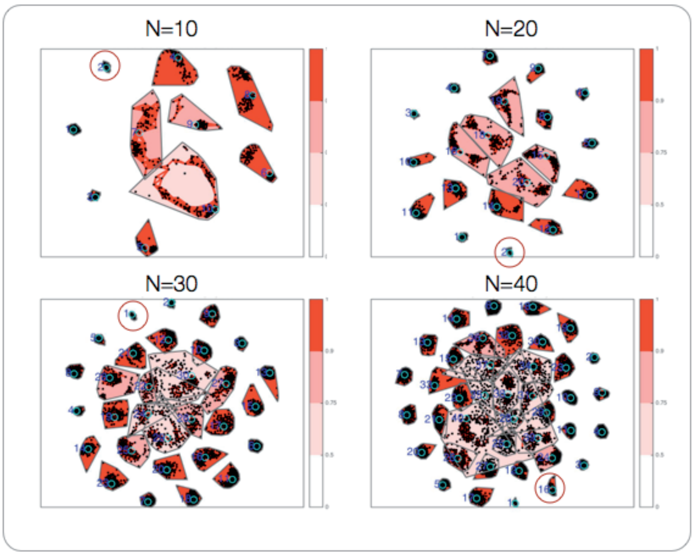

FIGURE 12 ICASSO clustered IC estimates (showing the four first IC decompositions, i.e., model orders from 10 to 40). The selected pulse clarity-driven ICs are indicated in circles. Dots represent the IC estimates per each ICASSO run. I_q values indicate from 0 to 1 the cluster compactness (zero indicates an unreliable IC estimate, one indicates the IC is stable; color online).

Results: ICA revealed significant differences in pulse clarity processing between musically trained and untrained participants, which were therefore likely attributable to musical expertise. Examination of the IC time courses across model orders indicated that nonmusicians' brain activity was overall significantly better predicted by the stimulus' pulse clarity than musicians' (see Figure 14). This supports the notion that musicians possess improved models of pulse clarity, which do not fit the model of pulse clarity derived from the acoustic stimulus, and thus correlations would be expected to be low between musicians' responses and the temporal evolution of pulse clarity given by the model. It can also be concluded that nonmusicians' internal model of pulse clarity relies on the stimulus' acoustical content to a greater extent than musicians'. These inferences are in line with evidence stressing intense musical training as a crucial factor that shapes beat processing.

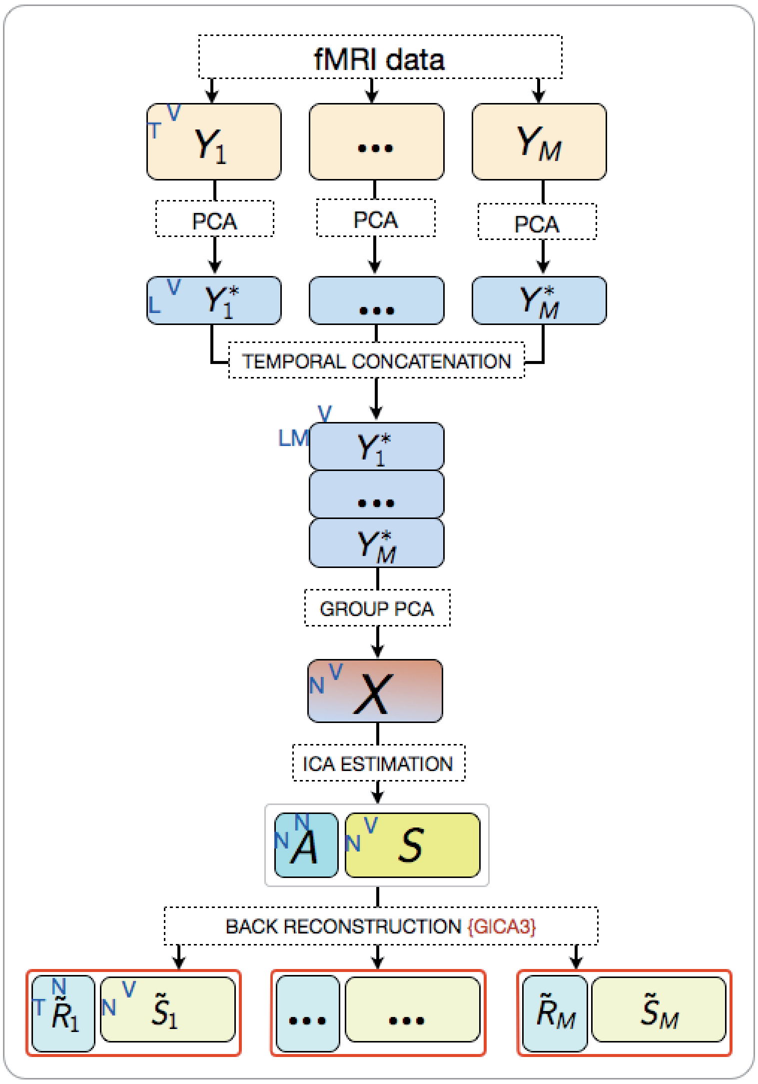

FIGURE 13 Pipeline of the different steps of the ICA approach used. $\boldsymbol{Y}$ denotes the subject data. $\boldsymbol{Y^*}$ is the subject-level reduced data. $\boldsymbol{X}$ is the group PCA-reduced matrix. $\boldsymbol{A}$ is the mixing matrix and $\boldsymbol{S}$ contains the N independent components. $\tilde{\boldsymbol{S}}$ denotes the subject-specific IC spatial maps and $\tilde{\boldsymbol{R}}$ contains their associated IC temporal courses. Abbreviations: M: number of participants; L: size of subject level PCA reduced time dimension; K: number of fMRI time points; V: number of voxels; N: number of estimated ICs.

Examination of the different spatial components associated with pulse clarity processing revealed consistent action-perception networks across model orders, which seemed to reflect different functional hierarchies in the brain networks responding to pulse clarity processing during continuous, real-world music listening (see Figure 15). The observed networks at lower model orders comprised auditory-motor areas, while at higher model orders they recruited mainly auditory areas. The polarity of the constituent areas of the network was highly consistent across model orders, with auditory areas showing positive sign, and somatomotor and cerebellar areas showing negative sign. This could denote an excitatory-inhibitory response within the network. These results are in line with previous findings (Chen et al., 2008, 2006; Grahn, 2009; Grahn & Rowe, 2009; Kung et al., 2013; Zatorre et al., 2007), particularly at low model orders (20 and 30), where auditory cortex along with basal ganglia (BG) areas, premotor cortex (PMC) and supplementary motor area (SMA), were observed among other areas (somatosensory cortex, Rolandic operculum, motor cortex and cerebellum).

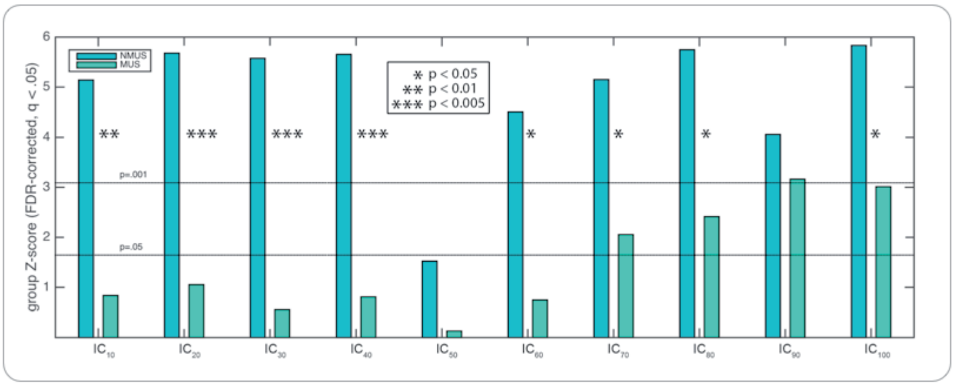

FIGURE 14 Pulse clarity-driven IC temporal courses per group. Significant between-group differences are also indicated.

GLM analyses were consistent and overlapping with ICA results. In non-musicians only, regional activity significantly and positively correlated with pulse clarity. This activity was constrained only to the auditory cortices. Thus, in comparison, ICA exposed areas hidden from GLM analyses.

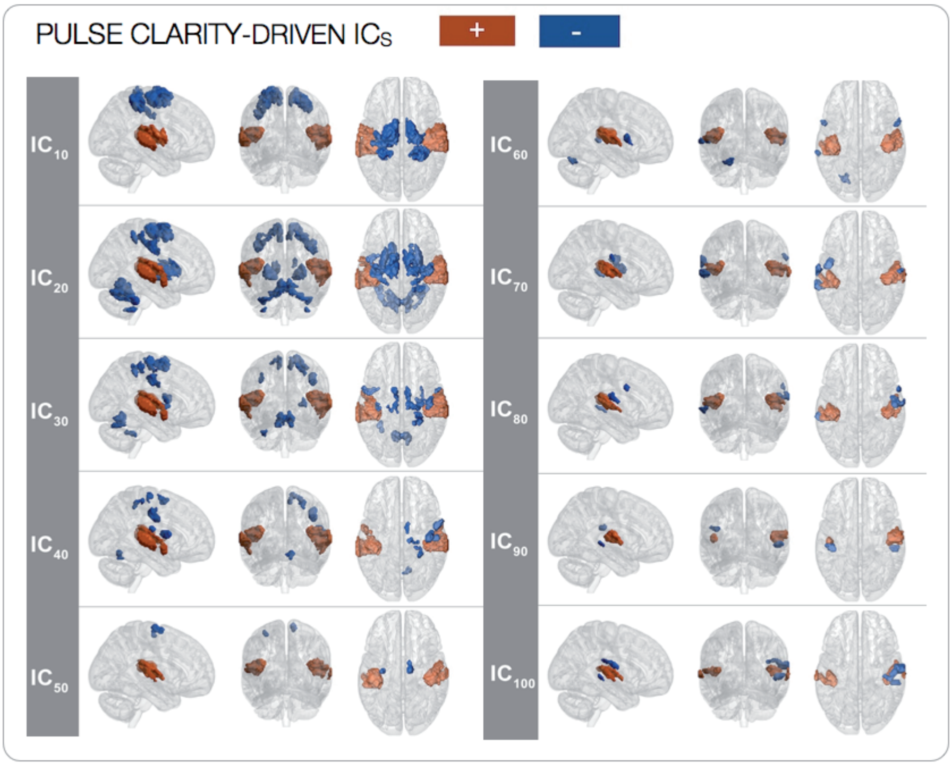

FIGURE 15 Pulse clarity-driven IC spatial maps. Abbreviations: + (plus): positive correlation; - (minus): negative correlation; LAT: lateral view; POS: posterior view; SUP: superior view; L: left; R: right; S1: primary somatosensory cortex; S2 secondary somatosensory cortex; HG: Heschl's gyrus; PT: planum temporale; ROper: Rolandic operculum; pSTG: superior temporal gyrus (posterior); aSTG: superior temporal gyrus (anterior); PMC: premotor cortex.

4 METHODOLOGICAL CONSIDERATIONS

4.1 Nonparametric methods for significance estimation

According to Nichols & Holmes (2002), nonparametric tests require minimal assumptions for validity and provide a flexible and intuitive methodology for the statistical analysis of data from functional neuroimaging experiments, at some computational expense. Traditionally, statistic images in fMRI are scrutinized for significance using parametric approaches (Friston et al., 1995; Worsley, Evans, Marrett, & Neelin, 1992), which assume a specific shape of the probability distribution of the voxel intensities in the statistic image. In those cases where parametric assumptions are questioned, the nonparametric methods provide the only valid and almost exact analysis (Holmes, Blair, Watson, & Ford, 1996). At worst, nonparametric methods may provide validation. The main drawback of such approaches constitutes the computational demand that they impose. In the current research work, nonparametric approaches were used to compute the statistical significance of some of the parameter estimates. Numeral simulations were run using the Taito HP super cluster[3].

4.1.1 Effective degrees of freedom

The distribution of a statistic depends on the number of *N* independent observations or associated effective degrees of freedom (DoF), which denotes essentially the amount of information on which an estimate is based. When working with fMRI time series, data independency is no longer a valid assumption. Detecting significant correlations in fMRI data increases with smoothness, to the extent that intrinsic autocorrelations lead to high test statistics even in the absence of activation (Friston, Jezzard, & Turner, 1994). The temporal autocorrelation of the fMRI scans in combination with the use HRF-convolved regressors

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[3] taito.csc.fi; CSC - IT Center for Science Ltd., administered by the Ministry of Education, Science and Culture of Finland. Taito provides an environment for a wide range of scientific software packages, which require up to a few hundreds of cores per job.

for correlation analyses has an impact on the effective DoF (Worsley, 2005; Worsley & Friston, 1995), and thus an effect on the statistical inferences made from the data. To ensure that the assumptions underlying standard significant testing are satisfied, it is therefore necessary to consider this serial correlation in the fMRI time series to accordingly modify the number of DoF that will ultimately lead to detect significantly activated voxels.

The procedure performed to estimate the effective DoF of the correlation coefficients is a simple function of the number of time points and the temporal autocorrelation (Pyper & Peterman, 1998) shown in (5),

$$\frac{1}{df} \approx \frac{1}{N} + \frac{2}{N} \sum_{j=1}^{\infty} \frac{N-j}{N} \rho_{xx}(j) \rho_{yy}(j), \tag{5}$$

where N is the number of observations, $\rho_{xx}(j)$ and $\rho_{yy}(j)$ are the autocorrelations of the inputs x and y, which represent the appropriate data for each study case. In Study I, for instance, x and y represent time series of a musical feature and a voxel, respectively, whereas in Study II, they represent a pair of homotopic voxel time series. The choice of lags j can influence type I error rates. The recommendation in Pyper & Peterman (1998) was followed, and $j = N/5$ was used, shown to provide the best combination of accuracy and precision in error rates with minimal variability across sample sizes and time series models. Effective DoF were computed for each participant by randomly selecting the inputs for N trials ($N > 1000$) and then averaging the estimates across participants.

4.1.2 Significance estimation of the ICCs

In Study I correlation coefficients were obtained between each of the original and replicated group activation spatial maps. To quantify their significance, a H_0 empirical distribution of coefficients was estimated using 'random' versions of each musical feature time series. Because merely randomizing the samples in the time series does not preserve its temporal dependencies, leading to biased estimates, a phase-scrambling procedure (Ebisuzaki, 1997; see 4.1.5) was used in order to preserve the temporal smoothness of the data. According to this approach, the phases of the musical feature time series are scrambled in the frequency domain and then inverse-transformed to the time domain. This results in a time series with the same autocorrelation function (ACF) as the original series and a different time-domain structure. This newly created variable was then correlated against each of the participants' fMRI time series in both original and replicated data, and the final group spatial maps were correlated against each other yielding a correlation coefficient. This procedure was repeated 50000 times to create a H_0 distribution of ICC values from which to derive the significance of the ICCs.

4.1.3 Significance estimation of the Dice coefficients

Dice coefficients were used to estimate the degree of spatial overlap at increasing proportions of the most significant voxels between the original and replicated spatial maps. In order to assess the significance of the resulting overlaps, a similar approach was employed as in 4.1.2. The Dice coefficient was computed 1000 times for each musical feature time series and for each proportion, to derive a H_0 distribution of overlaps as a function of each of the increasing proportions. To assess the probability of getting the observed overlap between datasets for each of the proportions, the empirically derived overlap values were converted to Z-scores by subtracting their empirical means and then dividing by their empirical standard deviations.

4.1.4 The problem of multiple comparisons

Clusterwise thresholding approaches are increasingly used to tackle the multiple comparisons problem, i.e. the risk to make type I errors in large amounts of data (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). They estimate the probability that a cluster of size $\geq v$ has occurred by chance. A cluster is a number of adjacent voxels, each of which has exceeded a predetermined primary activation threshold (cluster-defining threshold). The cluster-wise method attempts to detect statistically significant clusters defined by a second threshold (cluster-size threshold) controlled by a predefined family-wise error (FWE) rate (Hayasaka & Nichols, 2003). Inferences on the cluster size threshold can be derived using parametric methods such as random field theory (RFT; Worsley et al., 1992), or by means of nonparametric methods (Nichols & Holmes, 2002).

Clusterwise thresholding does not consider voxels as independent units, but takes into account the activation of the neighbouring voxels, an advantage over voxelwise thresholding (Heller, Stanley, Yekutieli, Rubin, & Benjamini, 2006). It also has higher sensitivity over traditional, more stringent voxelwise correction methods, such as Bonferroni and RFT-based corrections, which increase type II errors (Nichols & Hayasaka, 2003). However, the cluster level inference has worse spatial specificity for large clusters (Nichols, 2012), because the H_0 of the entire cluster is accepted or rejected. If rejected, it can only be concluded that one or more voxels in the cluster is active.

In the present studies, a nonparametric clusterwise approach was used based on a combination of phase-scrambling and permutations. This was done to obtain an estimate of an ACF representative of a null distribution, and use it to generate random images $\boldsymbol{S}$ with the same spatial smoothness as the statistical image (SI) subjected to clusterwise correction (Ledberg, Åkerman, & Roland, 1998). It is crucial that the information about spatial smoothness is kept because it defines the CS distribution. Additionally, because the ACF cannot be estimated directly from the SI, as it contains the signal of interest and may affect the spatial dependency, new images $\boldsymbol{P}$ must be generated which contain no signal of interest. To this end, the statistical test that produced the statistical images is rerun several times using phase-scrambling (see 4.1.5) several times. For instance, in Study I the musical features time courses were phase-scrambled and voxelwise correlated against the fMRI data, whereas in Study II the functional symmetry maps were obtained by correlating the fMRI image with its own flipped and phase-scrambled image, after which a between-groups t-test statistical map was obtained. This produces an image identical to the SI in spatial spectral properties except it shows no stimulus-dependent activations. From the final image an estimate of the ACF filter kernel K can be computed as follows:

$$K = IFT\left|FT(\boldsymbol{P})\right|, \tag{6}$$

where *IFT* and *FT* denote the inverse Fourier transform and the Fourier transform, respectively. The average across all K is computed for greater accuracy in the K estimate, and used to generate random images ***S*** with the same spatial properties as the SI as indicated in (7)

$$\boldsymbol{S} = U * K, \tag{7}$$

where U denotes a normally distributed random image, and ***S*** is created by convolving U with the filter kernel K. $\boldsymbol{S}$ is then normalized to zero mean and unit variance, and thresholded according to the predefined cluster-defining threshold. A sufficiently large number of $\boldsymbol{S}$ images needs to be generated to create a reliable H_0 CS distribution, from which to estimate the critical cluster-size according to an appropriate FWE rate.

The clusterwise approaches used in Studies III and IV did not use phase-scrambling, but instead a bootstrap resampling technique, which was relatively less computationally intensive (except for the GLM approach in Study IV, for which phase-scrambling was also employed).

In Study III, the H_0 CS distribution was derived through bootstrap resampling group membership (musicians and nonmusicians), with replacement prior to performing t-tests between the randomized groups. Each resulting t-test map was thresholded at the selected alpha level. A sufficiently large number of iterations was run to derive a reliable critical cluster size. The whole procedure was repeated for each of the hippocampal seeds. Mixing experimental and control groups guarantees the estimation of a H_0 CS distribution.

In Study IV, the approach was to sample from the pool of 36 back-projected IC maps. For instance, for model order N, there were 36*N IC maps, from which 36 were drawn randomly with replacement, then t-tested and thresholded, from which the empirical CS distribution was generated after a number of iterations. This way a CS distribution could be derived for each model order. Bootstrap resampling from different ICs within a model order guarantees the uncorrelatedness of the spatial maps, while ensuring the consistent spatial autocorrelation structure among them.

4.1.5 Phase-scrambling method

This approach (also known as Fourier resampling) is a nonparametric method to create random time series with the same power spectra as the original series. To this end, it Fourier transforms the data, randomizes the phase components while keeping the magnitude of each frequency component, and then inverts the transform (Schreiber & Schmitz, 1996). Thus, the resampled series retains the same ACF as the original series. These are the steps:

1. Let $a(t)$ be the time series of interest, take the Fourier transform (FT) of $a(t)$:

$$F(k) = \int a(t) e^{-2\pi ikt} dt. \tag{8}$$

2. Convert to polar form:

$$F(k) = r_k e^{i\varphi_k}. \tag{9}$$

3. Randomize the phase at each frequency to create a Fourier transform $\tilde{F}(k)$ with the original transforms' power spectrum but with random phases.

$$\tilde{F}(k) = r_k e^{i\theta_k}. \tag{10}$$

θ random, uniformly distributed in $\left[0, 2\pi\right]$

4. Take the inverse Fourier transform (IFT) of $\tilde{F}(k)$, which gives $a(t)$, a random series with the same autocorrelation as the original series. The power spectra of the randomly generated and original time series are the same, except the phases of $a(t)$ are random.

$$\tilde{a}(t) = \int \tilde{F}(k) e^{2\pi ikt} dk. \tag{11}$$

4.2 ROI-based ICA

Spatial ICA (sICA) is the ICA variety typically performed in fMRI, which assumes that each voxel time series (observation) represents a linear mixture of a number of unknown hidden underlying source signals that are maximally statistically independent, as opposed to temporal ICA (tICA), for which temporal independence of sources is assumed. The main reason for this is computational feasibility: in fMRI the spatial dimension (number of voxels) is much larger than the temporal dimension (number of scans), which requires the computation of a covariance matrix on the order of N^2 (N = number of voxels; Calhoun, Adali, Pearlson, & Pekar, 2001). This linear mixture of underlying source signals can be expressed as the product of the sources by a mixing matrix as in (4). The goal of ICA is to separate the sources ($\mathbf{S}$) from the linearly mixed fMRI signals ($\mathbf{X}$), in search of a solution in the form $\mathbf{S} = \boldsymbol{W}\mathbf{X}$, where $\boldsymbol{W} \approx \boldsymbol{A}^{-1}$. The source estimates given by ICA are called ICs (independent components). SICA assumes independence of spatial brain activations, where the *k*th row of $\mathbf{S}$ indexes the ICs, and the *k*th column of $\boldsymbol{A}$ indexes its associated temporal courses, which describes the relative projection weights of the corresponding spatial ICs at each time point. It then defines ICs by grouping brain regions showing synchronised source signals (Calhoun, Liu, & Adali, 2009; McKeown et al., 1998; McKeown & Sejnowski, 1998). Different processes may be captured by each IC, such as functionally relevant networks (e.g., visual, auditory or motor), physiological processes (e.g., breathing), and artefacts (e.g., head motion; Damoiseaux et al., 2006).

As stated above, the independence criterion is the guiding principle of ICA, and ICs are found by maximizing their statistical independence. Statistical independence means that that the value of any of the ICs provides no information on any value of the other ICs, and this characteristic can be defined by the probability densities. Two random variables x and y with probability densities $p_x(x)$ and $p_y(y)$ are independent if the joint density exists

$$p_{x,y}(x, y) = p_x(x)p_y(y). \tag{12}$$

The fundamental restriction to ICA is that the independent components must be nongaussian for ICA to be possible, because the matrix $\boldsymbol{A}$ is not identifiable for Gaussian independent components (with the exception of a maximum of one Gaussian component; Hyvärinen & Oja, 2000). This principle draws from the central limit theorem (CLT), which states that the sum of N independent random variables approaches a Gaussian distribution as $N \rightarrow \infty$. Thus, if mixed observations become more Gaussian than any of the independent sources, it is possible to find an unmixing matrix $\boldsymbol{W} \approx \boldsymbol{A}^{-1}$ that maximizes the nongaussianity of $\boldsymbol{W}\mathbf{X}$.

A classical measure of nongaussianity is kurtosis (the normalized fourth central moment), which measures the tailedness or flatness of a probability distribution[4]. However, as noted by Hyvärinen (1999), kurtosis is sensitive to outliers and thus not a robust method to estimate nongaussianity. A fundamental theorem in information theory is that a *Gaussian variable has the largest entropy among all random variables of equal variance* (Cover & Thomas, 2012; Hyvärinen & Oja, 2000), thus the information-theoretic quantity called negentropy—a robust measure of distance to normality based on differential entropy—can be used to compute nongaussianity. Negentropy has the convenient property of being al-

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[4] A Gaussian distribution has zero kurtosis.

ways non-negative for nongaussian distributions, and equal to zero if and only if the measured distribution is Gaussian. Other quantitative measures of independence exist, such as minimization of mutual information, maximum likelihood estimation, or the infomax principle; however, they lead to the same principle of finding the most nongaussian directions (Hyvärinen, Karhunen, & Oja, 2001).

All ICA methods are iterative optimization processes aimed at finding an unmixing matrix that maximizes an objective function that measures the degree of independence of the estimated components $\mathbf{S} = \boldsymbol{W}\mathbf{X}$. In the case of the FastICA algorithm, non-gaussianity (the objective function) of the source estimates is maximized using approximations to negentropy, since its calculation requires the specific probability density functions (Hyvärinen, 1999; a Hyvärinen & Oja, 2000). Iterative algorithms such as FastICA have been reported to yield consistent results for ICs of interest, which increase the confidence in the use of ICA for fMRI analysis (Correa, Adali, & Calhoun, 2007).

ICA analysis usually undergoes a preprocessing stage, which includes centering, dimension reduction, and whitening in order to reduce the complexity and data redundancy for the subsequent ICA decomposition. In group ICA analysis of multi-subject fMRI data, two stages of dimension reduction prior to applying ICA are often performed to reduce the computational load and avoid overfitting (Calhoun et al., 2001; Calhoun, Adali, Pearlson, & Pekar, 2001). This is typically done using PCA, which captures most of the variability in the data while reducing their dimension. First, a subject-level dimension reduction is performed in the temporal domain, followed by a second dimension reduction stage, for which the reduced data from all subjects are concatenated. This is necessary to make the data dimensions match the number of ICs estimated by ICA (Erhardt et al., 2011). Once the unmixing matrix $\boldsymbol{W}$ has been estimated, subject-specific IC spatial maps and associated temporal courses can be reconstructed, enabling statistical inferences between groups, for which various multi-subject ICA approaches have been proposed (Calhoun et al., 2001; Guo & Pagnoni, 2008; Schmithorst & Holland, 2004). Among the existing methods, recent evidence (Erhardt et al., 2011) suggests that GICA3 provides both the most robust results with the most intuitive interpretation derived from its mathematical properties, such as the aggregate IC spatial map being the sum of the back-reconstructed subject-specific spatial maps.

Because ICA operates with high order statistics to achieve independence of source signals, it enforces stricter criteria for spatial independence among IC maps than e.g., PCA, which separates the sources by uncorrelating the data. Thus, PCA estimates only uncorrelated and not independent components. This could explain why ICA seems to outperform PCA in determining the spatio-temporal extent of task-related activation, with increased robustness to the addition of simulated noise across trials (McKeown et al., 1998).

4.2.1 Comparison with the General Linear Model (GLM)

ICA seems to have a higher sensitivity for detecting task-related changes in fMRI signal compared to the widely used univariate GLM-based approach (Xu, Potenza, & Calhoun, 2013), which aims at fitting an a priori temporal model at each voxel by minimizing the least squared error. The GLM model for a hemodynamic response variable x_{ij} at given voxel $j = 1,\ldots,N$, at time point (scan) $i = 1,\ldots,M$ is

$$\mathbf{x}_{ij} = \mathbf{g}_{i1}\beta_{1j} + \mathbf{g}_{i2}\beta_{2j} + \cdots \mathbf{g}_{iK}\beta_{Kj} + \mathbf{e}_{ij}, \quad (13)$$

where the coefficients $\mathbf{g}_{iK}$ are the K explanatory variables, $\boldsymbol{\beta}_{\mathrm{Kj}}$ are K parameter estimates for each voxel j, and $\mathbf{e}$ is the error term. Thus, only the activation modelled by the researcher can be studied (Friston et al., 1998). Accordingly, the higher sensitivity of ICA is a consequence of a stricter criterion for spatial independence between IC maps, which reduces noise in the final solution by separating artefactual and other physiological fluctuations from the fMRI signal of interest (McKeown et al., 1998).

As for seed-based connectivity methods, these investigate only bivariate (pairwise) relationships, in which the choice of a seed region is required. However, ICA is multivariate and thus considers all reciprocal relationships between voxels simultaneously. Additionally, ICA requires no a priori, explicit temporal model of the signals to be extracted, and thus no need to specify the HRF-convolved stimulus-related neuronal activation or the selection of a seed voxel, because they are implicitly estimated in the ICA algorithm (Calhoun & Adali, 2006; Svensén, Kruggel, & Benali, 2002).

Findings from GLM analyses are often inconsistent, which may expose the limitations in sensitivity and specificity of the GLM approach resulting from fundamental brain properties (i.e., functional heterogeneity and balanced excitation and inhibition; Xu et al., 2015). Similarly, because GLM-based approaches cannot segregate the signal mixture from each voxel into source signals, they are not suited to detect overlaps of functional networks and their temporal course modulation by cognitive tasks. Thus, GLM approaches conform to the modular view of brain functional organization. However, the overlap of functional networks with different temporal courses and their modulation by cognitive tasks is critical for understanding brain functional organization (Fuster, 2009; Quintana & Fuster, 1999). ICA methods, conversely, are capable of disentangling signal mixtures. It is thus not surprising that ICA may help reconcile inconsistent GLM findings due to its suitability in detecting large-scale functional network overlaps, and thus compatibility with this general property of brain functional organization as evidenced recently (Xu et al., 2016; Xu, Zhang, et al., 2013). Finally, as a consequence of its inherent properties, ICA is increasingly gaining interest in the context of fMRI naturalistic paradigms, providing a framework for reliable analyses of complex stimuli with increased ecological validity (Bartels & Zeki, 2005; Bartels & Zeki, 2004b; Malinen et al., 2007; Wolf et al., 2010).

In sum, although ICA is not model-free because it requires certain assumptions (e.g., independence), it is in general more flexible with fewer assumptions than other approaches, and constitutes a powerful complementary tool to voxelwise analyses.

4.2.2 Application of ICA to a region of interest

In Study IV ICA was applied in a constrained, hypothesis-driven ROI. Several studies have shown that localization of fMRI data to specific brain region analysis provides finer functional subdivisions (Beissner, Schumann, Brunn, Eisenträger, & Bär, 2014; Formisano, Esposito, Di Salle, & Goebel, 2004; Igelström, Webb, & Graziano, 2015; Sohn, Yoo, & Jeong, 2012). A ROI-based ICA approach improves the separation and anatomical precision of the identified spatial components and enables only informative signals with respect to potentially interesting sources to be included in the analysis since (a) the brain volume does not affect the number of obtained components, and (b) informative signals with respect to potentially interesting sources are included in the analysis, thus excluding contributions otherwise used to separate non-interesting processes (e.g., artefacts; Beissner et al., 2014; Formisano et al., 2004; Sohn et al., 2012). However, in order for ROI-based ICA analyses to be beneficial, it is essential to have prior knowledge about the localized region before performing analyses (Sohn et al., 2015).

4.2.3 The problem of model order selection

The problem of model order selection refers to the assumption of the number of sources to be extracted prior to performing ICA. In ICA, at least N observations (fMRI time points or scans) are needed to recover N sources. Although rules of thumb and recommendations exist in the literature (Abou-Elseoud et al., 2010; Onton & Makeig, 2006; Särelä & Vigário, 2003), as well as model order selection criteria (Akaike, 1974; Rissanen, 1983), the question of how to estimate the appropriate true number of sources is still under investigation.

If the dimensionality of the data is underestimated, valuable information may be discarded. However, overestimation may return a large number of ICs that distort functional subdivisions due to underconstrained estimation and overfitting (Beckmann & Smith, 2004), while, at the same time, the repeatability or robustness of the IC estimates is degraded (Li, Adali, & Calhoun, 2007). By altering the model order, different networks or subdivisions of networks can be identified (Kalcher et al., 2012). At higher model orders, ICs show a finer-grained subdivision of networks because the ICA algorithm is forced to find more local nongaussianity maxima, whereas low model orders give a broad picture of large-scale brain networks (Abou-Elseoud et al., 2010). Thus, model order selection has a crucial impact on the spatial characteristics of the identified functional networks (Abou-Elseoud et al., 2011).

Parcellation of functional networks at different model orders may be explained from a graph theoretical perspective, which suggests a small-world and scale-free organization of the functionally connected human brain (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Buckner et al., 2009; Sporns & Zwi, 2004; Stam, 2004; van den Heuvel, Stam, Boersma, & Hulshoff Pol, 2008;

van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009). Small-worldness guarantees high efficiency at different spatial and temporal scales with a very low wiring and energy cost (Guye, Bettus, Bartolomei, & Cozzone, 2010; Lang, Tomé, Keck, Górriz-Sáez, & Puntonet, 2012). According to Abou-Elseoud et al. (2010), large networks observed at low model orders may be show weaker connections compared to nonbranching ICs found at higher model orders, with particular spatio-temporal profiles not shared by any other ICs and therefore more functionally independent. Thus, functional connectivity differences are associated with changes in ICA model order. From the point of view of differences between or within groups of subjects, some model orders may accentuate between-group or within-group differences compared to other model orders (Abou-Elseoud et al., 2011). This means that model order can convey information about the hierarchy level within the network where differences are maximized.

Taking into consideration all of the above, it seems sensible to suggest that, at least with neuroimaging data, there may not exist such a notion as a right model order, and it would depend on the level of depth or breadth chosen when investigating functional networks along with group- or task-related differences. This was the stance taken in Study IV for presenting findings within a range of model orders.

5 DISCUSSION

5.1 Main findings

5.1.1 Reliability of the naturalistic listening paradigm

Study I concluded that brain responses to timbral (low-level) feature processing (Fullness, Brightness, Timbral Complexity, and Activity) were replicated with a higher degree of reliability than those to tonal and rhythmical (high-level) features (Key Clarity and Pulse Clarity). The latter may depend on cognitive mechanisms associated with increased participant-dependent variability in the brain signal, which may reduce replicability. Other alternative explanations for the low replicability of the high-level musical features could lie in the use of an unsuitable statistical approach for investigation of this phenomenon (e.g., isomorphic vs. second-order isomorphic approach).

The most reliable areas across all musical features (except for Key Clarity) were found within the auditory cortices, with a right-ward asymmetry in the case of Pulse Clarity and Activity. The case of Key Clarity seemed different because it was most replicable for voxels with a lower significant level compared to the other musical features. We argue that this less significant map of reliable areas could denote meaningful information in the encoding of tonal feature processing. Multivariate studies in neuroscience have recently observed that levels of activity considered subthreshold in univariate analysis succeed in retrieving relevant stimulus-specific information (Harrison & Tong, 2009; Reuter-Lorenz & Sylvester, 2005; Riggall & Postle, 2013; Serences, Ester, Vogel, & Awh, 2009; Sreenivasan, Vytlacil, & D'Esposito, 2014).

The choice of a measurement tool to quantify reliability is a crucial question that depends on the specific aspect of reliability targeted. In the present approach, similarity between both experiments was estimated by (a) comparing the whole-brain spatial extent of activations at the group level (by means of the interclass correlation coefficient), and (2) identifying the anatomical areas of most significant overlap for each of the features (by means of the Dice's coefficient), thus characterizing the stability over the extent of the most significant activations across experiments. An advantage of these approaches is that they do not only examine above-threshold activity, and are therefore not reliant on arbitrary rules which determine whether or not a voxel is “active” (McGonigle et al., 2000).

Finally, because unreliable results render the validity of any scientific endeavour meaningless (Bennett & Miller, 2010), the successful replication provided support for the use of naturalistic stimulation paradigms in music neuroscience. This finding encourages scientific practices towards more real-life lab environments which could capture the complexity of real-world experiences of music listening, a crucial step when aiming at modelling how the brain interacts with the world. However, non-replicable findings are not untrue by default, because they may expose subtleties in the experimental design (e.g., variables that were not considered in the first experiment). Therefore, replication is always positive even if not successful. However, encouraging replication is a futile endeavour so long as mainstream scientific publishing continues to promote and reward novel and surprising results over studies that tackle other aspects of scientific investigation.

5.1.2 Functional symmetry and musical expertise

Study II revealed different symmetry profiles as a function of musical training: increased functional symmetry was found in musicians and keyboard players compared to nonmusicians and string players, respectively. Overall, results support the role of specific posture and kinematics in bimanual instrument training along with unequal visual-processing requirements of instrument score-reading and hand monitoring as drivers of this symmetry. All in all, findings suggest a crossmodal transfer of symmetry from sensorimotor to perceptual processing systems, because the apparent effects of motor training within the motor system become evident in the brain responses to music perception. It is speculated that this effect results from action-perception coupling through life-long instrument training.

Musicians vs. nonmusicians: Compared to nonmusicians, musicians’ increased symmetry was largely localized within the somatosensory and motor control areas. These group differences may be largely driven by musicians’ hand and finger dexterity (Hyde et al., 2009). Enhanced symmetry within the motor system may thus underlie a more efficient hemispheric communication in musicians driven by the demands of musicianship, such as bimanual coordination of finger movements, which would require greater communication between bilateral motor regions for the necessary speed and efficiency required during music performance.

Keyboard vs. string players: Keyboardists showed more pronounced symmetry mainly in visual areas and, to a lesser extent, in somatosensory areas compared to string players. These group differences could be instrument-specific. Both keyboard and string instrument playing demand fine motor skills and bimanual hand coordination. However, string instrument playing enforces not only a more asymmetric position and movement between bilateral hands and fingers, but also a strict asynchrony between left-hand finger movements and right-hand bowing. This would account for the enhanced functional symmetry observed in keyboardists' motor-related areas. Moreover, left-hand and fingers' asymmetry in the contralateral somatosensory cortical representations (Elbert et al., 1995; Schwenkreis et al., 2007) would only amplify this effect. More demanding hand-eye coordination skills in keyboard playing may be accompanied by efficient hemispheric communication (resulting e.g., from multiple-part reading, which requires transfer of visual information to contralateral motor outputs, but also from hand monitoring). This may therefore account for keyboardists' prominent symmetry in the visual system compared to string players, and is in accordance with previous findings on enhanced symmetric visual responses in pianists (Patston et al., 2007).

Group differences in callosal size: while the posterior section of the corpus callosum was larger in musicians compared to nonmusicians, there was no significant difference between keyboard and string players. Previous studies observed a significant difference in the anterior section of the callosum (Lee et al., 2003; Schlaug et al., 1995). Despite studies linking volume of corpus callosum, amount of fibres crossing through it, and enhanced interhemispheric connectivity (Aboitiz et al., 1992; Jaencke & Steinmetz, 1994; Witelson, 1985), no correlation was found between callosal size and functional symmetry for any of the groups compared. It should be noted that the literature on this issue presents conflicting results (Banich & Shenker, 1994; Pizoli et al., 2011; Reilly et al., 2013; Tyszka et al., 2011; Uddin et al., 2008; Wang et al., 2014).

5.1.3 Cerebello-hippocampal connectivity

Study III revealed greater CER-HIPP functional integration in musicians, modulated by the degree of predictability in the music during music listening, when compared to controls. More specifically, musicians' CER-HIPP connectivity increased as information content in the music (i.e., degree of predictability) decreased, which was hypothesized as resulting from musicians' improved predictive listening accuracy. This hypothesis was motivated by results from Onuki et al. (2015), who found CER-HIPP coupling to be an indicator of participants' accurate predictions based on integrating both spatial and temporal information. Because musicians are known to posses optimized predictive models of musical structure over nonmusicians, which facilitates anticipation of musical events (Drake & Palmer, 2000; Ericsson & Towne, 2010; Hansen, Vuust, & Pearce, 2013; Lehmann & Gruber, 2006), especially in low information contexts (Hansen & Pearce, 2014; Hansen et al., 2013), this CER-HIPP connectivity may be indicative of musicians making more accurate predictions than controls as they listen to music. This is in accordance with Onuki et al. (2015)'s results, denoting optimized behaviour as a consequence of predictive adaptation to musical structure. Moreover, this superior predictive ability may derive from action simulation mechanisms enacted spontaneously during music listening, due to years of intensive musical training, and rooted in the experience-dependent coupling of perception and sound-producing actions. This ability is also evidenced by the narrower temporal auditory-motor integration window observed in musicians compared to controls when judging an action and its resulting effect, potentially due to more refined temporal prediction abilities (van Vugt & Tillmann, 2014). Moreover, musicians, by virtue of their musical training, tend to perceive auditory signals as intentional motor acts to a greater degree than nonmusicians (Bangert & Altenmüller, 2003; Bangert et al., 2006; Haslinger et al., 2005).

Group differences in the functional integration of the CER-HIPP network may therefore evidence for the impact of musical training on the listeners' underlying strategies or modes of music listening. Accordingly, our findings may indicate that musicians' spatio-temporal prediction of fine motor actions, as observed in the CER-HIPP connectivity, can also occur during music perception through the process of action simulation.

The current results extend recent findings on the novel area of CER-HIPP interactions by using a perceptual setting that is predictive in nature (music listening) and advance the understanding of its integrative function in the context of prediction.

5.1.4 Pulse clarity processing

Study IV showed that musicians and nonmusicians process pulse clarity differently when listening to music. Particularly, nonmusicians' perception of pulse clarity seemed to be captured more reliably by the acoustic content of the music than musicians', given the high correlations between nonmusicians' brain responses and the pulse clarity model extracted from the musical stimulus. However, this model did not succeed in predicting musicians' brain responses as effectively. An explanation may lie in musicians' superior timekeeping abilities (Chen et al., 2008, 2006; Krause, Schnitzler, & Pollok, 2010; Pollok, Gross, & Schnitzler, 2006), advantageous for musical performance. As a consequence of life-long musical training, pulse clarity processing in musicians relies less on the stimulus properties and more on cognitive, top-down rules and processes of metricality, facilitating enhanced internal beat generation, which stands as a reliable marker of rhythmic skill (Grahn & Rowe, 2009). As for nonmusicians, they would employ Gestalt principles of temporal proximity to a greater extent, which are suboptimal for accurately encoding temporal information (Chen et al., 2008).

A comprehensive ICA decomposition of the data across several model orders revealed the corresponding functional networks subserving the processing of pulse clarity during music listening. Overall, the associated spatial maps comprised a large-scale network of auditory and motor-related areas, with higher model orders exposing fine-grained, small-scale networks, consisting almost exclusively of the auditory cortices. These could be taken to denote universal main hubs for a wider population, given the significant correlations with both musicians' and nonmusicians' temporal courses. Because ICA does not make a priori assumptions on the number of sources, it is possible to find multiple sources underlying a single component. Thus, lower model orders, enforcing the assumption of a smaller number of sources, tend to group singular ICs that at higher model orders separate into their single functional units. Model orders therefore represent the hierarchical organization or clustering of the functional networks. The large-scale networks observed at lower model orders represent brain networks underpinning exclusively nonmusicians' processing of pulse clarity, as musicians' correlations between their temporal courses and pulse clarity did not achieve significance at these low model orders.

One feature of the observed networks was their consistent polarity for all decompositions. Positive sign was largely found for the auditory areas, whereas negative sign was observed for the remaining circuitry. These results may be construed as an action-perception functional network during pulse clarity processing that maintains an excitatory-inhibitory relationship.

A key strength of the present study was the derivation of functional networks at a range of assumed number of sources. In addition, the fact that the associated spatial maps were spatially consistent across decompositions supports the reliability of the approach. The complementary GLM analysis served as an additional reliability check, by demonstrating the power of the ICA approach, which enabled the detection of networks undetectable through GLM.

5.2 Main contributions of the thesis

The main contributions of this dissertation are summarized as follows:

Contributions to knowledge:

- Low-level (timbral) features are reliably replicated compared to high-level (tonal and rhythmical) features; a finding perhaps accountable for by the sensitivity of the latter to large between-participant variance in the brain responses to music, or alternatively by the use of an inappropriate statistical approach or acquisition method (e.g., insufficient temporal resolution of the hemodynamic responses).
- Key Clarity processing can be successfully replicated in areas considered subthreshold in univariate analyses, exposing that relevant stimulus-specific information may be encoded in so-called subthreshold activity.
- A dependency between musical training and functional symmetry exists as observed during music listening: symmetrical actions derived from musical training manifest in symmetrical brain responses while listening to music. Specific posture and kinematics in bimanual instrument training along with unequal hand-eye coordination requirements may be potential drivers of this symmetry.
- Findings suggest a crossmodal transfer of symmetry from sensorimotor to perceptual processing systems: the apparent symmetry effects of mo-

tor training within the motor system manifest in the brain responses to music perception.

- Findings have broad implications for understanding how experience in one modality (e.g., motor/visual processing) may alter the neural processing in another modality (auditory perception). From a broader perspective, it highlights the significance of our multimodal musical experience in how our brains respond to music.
- Musicians exhibit stronger CER-HIPP functional integration compared to controls as information content in the music decreases (i.e., predictability increases), which may result from musicians' improved predictive listening accuracy, as suggested by previous literature. As a novel finding, it requires further study and replication for validation of the assumptions. More generally, these current findings advance the understanding of cerebellar integrative function in the context of prediction.
- Pulse clarity-processing differences exist between musically trained and untrained individuals when listening to music, as inferred in a data-driven manner, providing support for musicians' improved predictive models of beat induction.
- Pulse clarity processing is subserved by an action-perception functional structure consistent with previous neuroimaging work on rhythm processing. This functional structure reflects a hierarchy of large-scale networks of cerebellar, basal ganglia, cortical somatomotor and auditory areas, and small-scale networks involving mainly auditory cortices as potential main hubs and common to both musicians and nonmusicians.
- The functional networks implicated in pulse clarity processing reflect a polarity, wherein auditory (positive sign) and somatomotor (negative sign) regions are hypothesized to maintain an excitatory-inhibitory relationship.

Methods-related contributions and recommendations:

- Support for the validity of the naturalistic listening stimulation paradigm in the field of cognitive neuroscience, reinforcing the use of real-life lab settings to capture the complexity of the real world in order to model how the brain interacts with it.
- Support for the use of reliability assessment in fMRI studies through replication.
- Novel approach in the study of rhythm processing by using ICA within a ROI informed by previous findings in combination with acoustic feature extraction within a naturalistic auditory stimulation framework (free-listening to continuous real-world music), and further reliability check from GLM analyses.

- The inclusion of comprehensive results derived from a continuum of assumed dimensionalities for the ICA data decomposition has not been used previously in music neuroscience to study neural correlates of musical percepts. This procedure provides valuable information by exposing a finer-grained and hierarchical functional organization of the networks involved in the phenomenon under investigation.
- Recommendation towards the use of reliability measures that estimate similarity of results based on ranked and continuous-valued (unthresholded) data (which take into account the overall shape of the activation map), rather than based on a binary division of the data by some arbitrary threshold. This attenuates the effect of differential SNR between experiments.

6 CONCLUSION

The inferences presented in this work speak to musicians' increased sensorimotor functional integration in networks known to subserve aspects of the musical experience. Particularly, this thesis has implications for training-induced crossmodal reorganization. The functional adaptations observed in musicians during mere music listening can be understood as crossmodal brain adaptations likely resulting from an increased use-dependent plasticity.

This work contributes to the growing body of neuroscientific studies by complementing and extending previous work in music neuroscience. It also outlines a framework for the exploration and hypothesis-testing of neuroscientific knowledge relating to the brain-music relationship in listeners. The new evidence brought by the present findings, as well as the ideas derived from the outlined experimental framework and analysis pipelines, should positively guide the generation and development of future testable hypotheses.

From a wider perspective, this work illustrates how music constitutes a rich framework to explore the phenomenon of plasticity. Understanding the impact and magnitude of musical experience on our music-listening brains will provide a more comprehensive account of the property of the brain to change itself.

YHTEENVETO (FINNISH SUMMARY)

Musiikillisen harjoittelun vaikutus aivojen integratiiviseen toimintaan musiikinkuuntelun aikana

Väitöskirjassa tutkittiin aivojen magneettikuvantamismenetelmää (fMRI) hyödyntäen aivoalueiden toimintaa musiikin kuuntelun aikana, ja vertailtiin aivojen aktiivisuudessa tapahtuvia eroja musiikillisesti koulutettujen ja kouluttamattomien kuulijoiden välillä.

Toistettavuustutkimuksen avulla haluttiin testata aiemmissa tutkimuksissa käytetyn naturalistisen koeasetelman luotettavuutta, jossa musiikin herättämiä aivovasteita tutkitaan tarkastelemalla aivoista mitatun aktiivisuuden välistä yhteyttä musiikillisiin piirteisiin. Onnistuneen toiston jälkeen dataa analysoitiin kolmessa tutkimuksessa, joista kukin tarkasteli eroavaisuuksia aivotoimintojen integraatiossa muusikoiden ja ei-muusikoiden välillä. Tutkimusten tulokset (a) korostivat eri instrumenttien soittamiseen liittyvän erilaisen posturaalisen ja kinemaattisen symmetrian vaikutusta musiikin kuuntelun herättämien aivovasteiden symmetriaan, tarjoten näin todistusaineistoa aisti- ja liiketoimintojen ja havaintojen prosessoinnin välisestä yhteydestä; (b) tarjosivat uudenlaista näyttöä pikkuaivojen ja aivoturson välisestä toiminnallisesta kytköksestä, joka liittyy muusikoilla musiikilliseen ennakoimiseen todennäköisesti aivojen toimintasimulaatiomekanismien kautta; (c) toivat näkyville erot musiikin pulssin selkeyteen liittyvässä prosessoinnissa muusikoiden ja ei-muusikoiden välillä, ja paljastivat toimintaan ja havainnointiin liittyvän hermoverkon limittyvän aivoalueisiin, jotka on aiemmissa tutkimuksissa havaittu olevan kiinteästi yhteydessä rytmin prosessoinnin kanssa.

Tutkimustulokset, jotka saatiin käyttämällä stimuluksena oikeaa musiikkia keinotekoisten ääniärsykkeiden sijaan, lisäävät ymmärrystä aivojen integratiivisesta toiminnasta musiikillisesti koulutetuilla ja kouluttamattomilla henkilöillä. Tämän väitöstutkimuksen tulokset tuottivat tietoa erityisesti musiikin harjoittelun vaikutuksista aistipiirit ylittävään aivojen muokkautumiseen. Tulosten perusteella voidaan tulevaisuudessa kehittää uusia testattavia hypoteeseja musiikin aivotutkimukseen.

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ORIGINAL PAPERS

I

THE RELIABILITY OF CONTINUOUS BRAIN RESPONSES DURING NATURALISTIC LISTENING TO MUSIC

by

Iballa Burunat, Petri Toiviainen, Vinoo Alluri, Brigitte Bogert, Tapani Ristaniemi,
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The reliability of continuous brain responses during naturalistic listening to music

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A B S T R A C T

Low-level (timbral) and high-level (tonal and rhythmical) musical features during continuous listening to music, studied by functional magnetic resonance imaging (fMRI), have been shown to elicit large-scale responses in cognitive, motor, and limbic brain networks. Using a similar methodological approach and a similar group of participants, we aimed to study the replicability of previous findings. Participants' fMRI responses during continuous listening of a tango Nuevo piece were correlated voxelwise against the time series of a set of perceptually validated musical features computationally extracted from the music. The replicability of previous results and the present study was assessed by two approaches: (a) correlating the respective activation maps, and (b) computing the overlap of active voxels between datasets at variable levels of ranked significance. Activity elicited by timbral features was better replicable than activity elicited by tonal and rhythmical ones. These results indicate more reliable processing mechanisms for low-level musical features as compared to more high-level features. The processing of such high-level features is probably more sensitive to the state and traits of the listeners, as well as of their background in music.

1. Introduction

Alluri et al. (2012) explored the neural correlates of music processing as it occurs in a realistic or naturalistic environment, where participants' only task is to attentively listen to the whole piece of music. They observed large-scale brain responses in cognitive, motor and limbic brain networks during continuous processing of low-level (timbral) and high-level (tonal and rhythmical) acoustic features using fMRI. This was among the first approaches at attempting to uncover the functional brain topology of musical processing by jointly drawing on computational feature extraction, behavioral, and brain-activity measures to isolate the variance associated with a number of musical features. These features, computationally extracted from a dynamic, complex stimulus, represent the basic musical dimensions of the piece and their use constitutes a central aspect of this naturalistic approach.

The use of parameterized stimuli has been critical for isolating relevant dimensions out of the multidimensionality inherent to natural phenomena. In music neuroscience, previous research has focused on identifying the functional neuroanatomy of particular musical percepts, like pitch (Patterson et al., 2002; Warren et al., 2003), tonality (Janata et al., 2002a; Janata et al., 2002b), rhythm (Chen et al., 2008; Grahn & Rowe, 2009), and timbre (Caclin et al., 2006; Halpern et al., 2004), using controlled auditory paradigms and simple stimuli at the expense of ecological validity. Although both traditional and naturalistic approaches are necessary, as they convey mutually different aspects about the phenomenon under investigation, the literature has to date focused on the former, while not giving a fair representation of the phenomenon of musical processing in the brain in more naturalistic environments.

Decoding perception using realistic settings represents a hard challenge. Music is multidimensional and all elements embedded in it change in parallel over time. Compared to controlled auditory stimuli used in most experimental settings, real music is both dynamic and more complex. While listening to it we process these elements in parallel and integrate them into coherent percepts over time (Bregman, 1994). This type of more ecological processing has been shown to engage activity that includes brain areas beyond the sensory domain (for

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instance, areas concerned with motor control; Hasson & Malach, 2006) not activated in traditional studies with static stimuli (Bartels & Zeki, 2004; Hasson et al., 2004). Moreover, the sensory dimension of the stimulus is neither disconnected from its cognitive and affective dimension, nor from its context-driven goal and function (Hasson & Malach, 2006). It is the integration and interaction of all these aspects which gives coherence to our experience (Johnson, 1987), and thus a controlled setting falls short of all this complex multidimensionality. Using more realistic environments can consequently have a strong impact in the associated neural and cognitive processing of information (Zaki & Ochsner, 2009). With the advance in computational methods, new approaches are available to study the neural processing of natural phenomena that have not been possible to study using conventional methods. The viability of using these computational approaches has been demonstrated in neuroimaging paradigms where participants are shown movies, evidencing the ecological importance of such approaches (Hasson et al., 2004; Hutcherson et al., 2005; Hasson et al., 2008). As a result, naturalistic paradigms in neuroimaging are becoming more technically feasible for studying human brain functions.

The study by Alluri et al. (2012) (hereafter referred to as “the original study”) involved the use of a continuous stimulus in a naturalistic listening environment at the expense of added complexity to identify the brain areas supporting the processing of individual musical features. The results showed large-scale activation in previously unobserved areas such as the cerebellum and the basal ganglia in response to timbral features and the limbic system in response to high-level features, demonstrating the relevance of applying a naturalistic paradigm to music research. However, scientific paradigms and findings are of little use unless their validity and reliability is widely accepted (Bennett & Miller, 2010). Reliability can be defined as the degree to which a result is replicable after repeated measurements. In neuroscience reliability is a measure of the replicability of an activation map. Neuroimaging studies on reliability of findings are still sparse (Chen & Small, 2007). Indeed, concerns about the low reliability of fMRI finding have been recently voiced by the neuroimaging community (Barch & Yarkoni, 2013). Among the causes for low reliability and high discrepancy of findings fellow scientists have brought to notice the pervasive low statistical power (Button et al., 2013), prevalence of false positives, and overestimated effect sizes (Vul & Pashler, 2012).

Different factors can influence fMRI reliability, including sample size (Thirion et al., 2007). The signal-to-noise ratio (SNR) of the acquired images is often a measure of the data quality in fMRI and therefore needs to be maximized. Even small modifications in the fMRI processing pipeline can also have an impact on the results (Shou et al., 2013). Additionally, other sources of variation in the results are the analysis methods and the individual traits of the subjects or even their current mental state (Krüger & Glover, 2001; Zilles & Amunts, 2013). For instance, differences in the global SNR could be influenced by attentional effort on the task being performed (Specht et al., 2003). Furthermore, when assessing the reliability of results, different methods target different aspects of the results (e.g., stability of significant voxels across trials, or average signal magnitude) (Bennett & Miller, 2010).

The replicability of these aspects can be assessed in a within-subject, inter-subject, or inter-stimulus manner. In other words, reliability can be measured by examining how the results remain stable across trials for the same subject, between different subjects, or for different stimuli. The inter-stimulus reliability of the present auditory naturalistic paradigm was assessed in Alluri et al. (2013) by means of a cross-validation procedure. Results revealed the common functional anatomy of music processing during naturalistic listening across different musical contexts. Here, we aimed to quantify the inter-subject replicability of the original findings by Alluri et al. (2012). In this replication experiment, the musical stimulus was identical and the methodological pipeline was similar. The demographics of the participant pool as a group were equivalent. We propose two interclass measures to assess the similarity of the resulting functional group maps derived from the two studies: (1) correlation of resulting whole-brain activation maps; (2) overlap of active voxels in maps thresholded at variable levels of significance. The first measure characterizes the similarity in terms of the overall shape of the activation map, and the second measure focuses on the areas of optimal reliability.

2. Material and methods

2.1. Participants

Eleven right-handed healthy participants (5 females; 29 ± 1.4 years old) with no history of neurological or psychological disorders and with formal musical training (styles: classical = 8, folk = 2, pop/rock = 1; instruments: keyboard = 6, percussion = 3, string = 2, wind = 2; mean starting age = 8.4 ± 5.7 years; mean total training = 15 ± 5 SD years; mean practice time = 2.5 ± 1.2 SD hours/day) took part in the fMRI experiment (see Table 1 for a comparison with the participant pool of the original study). This study was part of a larger project (“Tunteet”) including several experimental sessions, fMRI paradigms, as well as questionnaires, and whose findings will be reported in separate papers. The participants were screened for inclusion criteria before admission to the experiment (no ferromagnetic material in their body, no tattoo or recent permanent colouring, no pregnancy or breastfeeding, no chronic pharmacological medication, no claustrophobia) and upon admission to the experiment signed an informed written consent. The study protocol proceeded upon acceptance by the ethics committee of the Coordinating Board of the Helsinki and Uusimaa Hospital District.

2.2. Stimulus material

The musical piece used in the experiment was the tango *Adiós Nonino* with a duration of 8 min and 8 s by the Argentinean composer Astor Piazzolla (1921–1992). This piece of music had been selected in the original study for its appropriate duration and high variance in several musical features such as dynamics, timbre, tonality, and rhythm.

2.3. Procedure

Participants' brain responses were acquired while they listened to the musical stimulus following the protocol observed in the original study. Listening to the music was the only task of the study. Before entering the scanner room, the experimenter set up a 32-electrode electroencephalography (EEG) cap on the participants' heads. Preparation, which included fixing EEG electrode impedance outside the scanner and adjusting the stimulus level to a comfortable but audible loudness inside the scanner room (around 75 dB), lasted about 40 min. In the scanner, the participants' only task was to attentively listen to the

Table 1
Demographic data used in the original and replication studies.

	Original study	Replication
Number	11	11
Age	23.2 ± 3.7 years	29 ± 1.4 years
Gender	5 females	5 females
Music genre	Classical = 5	Classical = 8
	Folk = 2	Folk = 2
	Pop/rock = 4	Pop/rock = 1
Instrument	String = 4	String = 2
	Percussion = 3	Percussion = 1
	Wind = 2	Wind = 2
	Keyboard = 2	Keyboard = 6
Mean starting age	9.1 ± 3.4 years	8.4 ± 5.7 years
Handedness	9 right, 2 n/a	11 right
Total training years	16.1 ± 6 years	15 ± 5 years
Practicing time	2.5 ± 1.2 h/day	2.6 ± 2 h/day

music delivered via high-quality MR-compatible insert earphones while keeping their eyes open.

2.4. fMRI image acquisition and preprocessing

Scanning was performed using a 3 T MAGNETOM Skyra whole-body scanner (Siemens Healthcare, Erlangen, Germany) and a standard 20-channel head–neck coil, at the Advanced Magnetic Imaging (AMI) Centre (Aalto University, Espoo, Finland). Concurrent EEG was also acquired with BrainVision amplifier. The data will be reported elsewhere, not being of interest to the current study goal of fMRI signal reliability. Using a single-shot gradient echo planar imaging (EPI) sequence, thirty-three oblique slices (field of view = 192 × 192 mm; 64 × 64 matrix; slice thickness = 4 mm, interslice skip = 0 mm; echo time = 32 ms; flip angle = 75°) were acquired every 2 s, providing whole-brain coverage. T1-weighted structural images (176 slices; field of view = 256 × 256 mm; matrix = 256 × 256; slice thickness = 1 mm; interslice skip = 0 mm; pulse sequence = MPRAGE) were also collected for individual coregistration. Functional MRI scans were preprocessed on a MATLAB platform using SPM8 (Statistical Parametric Mapping), VBM5 for SPM (Voxel Based Morphometry (Ashburner & Friston, 2000); Wellcome Department of Imaging Neuroscience, London, UK), and customized scripts developed by the present authors. For each participant, low-resolution images were realigned on six dimensions using rigid body transformations (translation and rotation corrections did not exceed 2 mm and 2°, respectively), segmented into grey matter, white matter, and cerebrospinal fluid, and registered to the corresponding segmented high-resolution T1-weighted structural images. These were in turn normalized to the MNI (Montreal Neurological Institute (Evans et al., 1994)) segmented standard a priori tissue templates using a 12-parameter affine transformation. Functional images were then blurred to best accommodate anatomical and functional variations across participants as well as to enhance the signal-to-noise by means of spatial smoothing using an 8 mm full-width-at-half-maximum Gaussian filter. Movement-related variance components in fMRI time series resulting from residual motion artefacts, as assessed by the six parameters of the rigid body transformation in the realignment stage, were treated as regressors of no interest to exclude movement-related variance from the image time series. Next, a high-pass filter of 0.008 Hz was applied to the fMRI signal, followed by temporal filtering (Gaussian smoothing with kernel width = 4 s).

As we are comparing data across two studies, we tested for differences in the amount of head movement between the groups by means of an independent-samples *t*-test using participants' standard deviations of each of the 6 movement components. There were no significant differences at alpha = 0.05 for any of the movement components.

2.5. Acoustic feature components

The time courses of perceptually validated acoustic features from the stimulus (in the following referred to as 'acoustic components') were provided by the main author of the original study. These acoustic components ($n = 6$) correspond to the main timbral, tonal, and rhythmic features in the stimulus (Fullness, Brightness, Timbral Complexity, Key Clarity, Pulse Clarity, and Activity; see Alluri et al. (2012) for an in-depth acoustic description). The acoustic components underwent the same truncation as in the original study (first 13 and last 12 samples, corresponding to the first 4 scans excluded due to T1 stabilizing effects, plus subsequent 9 samples to avoid artefacts from the convolution operation; and the last 24 s of brain volumes corresponding to the applause from the live performance). Next, the acoustic component time series were convolved with a canonical double-gamma HRF and high-pass filtered to match the preprocessing of the fMRI data, as indicated in the original study. Lastly, the acoustic components were downsampled to .5 Hz to match the sampling rate of the fMRI scanner. The final time series had a length of 231 samples.

2.6. Data analysis

Pearson's correlation *r* coefficients were computed at participant level for each acoustic component against each voxel time course. These *r* coefficients were *Z*-Fisher transformed to make the sampling distribution approximately normal, and their significance was subsequently corrected for serial correlation using Pyper and Peterman's method (Pyper & Peterman 1998).

On the same lines of the original study, group-level analysis was carried out on these results to produce a group map of significant voxels. To this end, and following the approach described in Lazar (2008), Fisher's method (Fisher, 1950) was used to obtain the pooled group-level *Z*-map from the individual *p*-value images.

2.7. Estimates of reliability

Because the assessment of similarities between the results of the original and the present studies is between measurements from two different groups of participants, the measures we propose are interclass measures, i.e., they characterize the replicability of the activation maps obtained at the group level.

To compare the reliability of the resulting activation maps, we propose two interclass measures: (1) interclass correlation coefficient between each pair of continuous-valued (unthresholded) maps and (2) overlap of active voxels at variable levels of ranked significance. Both approaches attempt to overcome the drawback of examining exclusively above-threshold activity using one single threshold. This is highly reliant on a relatively arbitrary procedure for defining whether or not a voxel is active depending on whether its signal intensity exceeds a conventionally established statistical threshold in univariate analyses (McGonigle et al., 2000).

2.7.1. Spatial correlation of the whole-brain maps (interclass correlation coefficient)

The interclass correlation measure computes the similarity based on the whole extent of spatial activations for each pair of the acoustic components' maps. Thus, it is not based on a relatively arbitrary thresholding of the compared maps. We computed the Pearson's correlation coefficient between each of the original and replicated group activation maps. To quantify their significance, we subsequently estimated the distribution of these coefficients under the zero reliability assumption by permutation tests (non-parametric approach). In this non-parametric approach, a randomized version of a randomly chosen acoustic component is created using a random phase procedure (Ebisuzaki, 1997), by which the phases of the acoustic components' time series are phase-scrambled in the frequency domain. This preserves the autocorrelation of the original series, but not its original time-domain structure. This newly created variable was then correlated against each of the participants' fMRI time series (the original data was provided by the main author of the original study). Finally, each groups' maps were averaged, and subsequently correlated against each other. This procedure was repeated 50,000 times, yielding a H_0 distribution of correlation values from which to derive the significance of the interclass correlation coefficients.

2.7.2. Overlap of active voxels between maps (Dice coefficient)

This approach consists of taking a proportion of the most significant voxels for each pair of compared maps, and computing the Dice overlap coefficient (Dice, 1945) between them.

The Dice coefficient is computed as shown in Eq. (1):

$$s_{xy} = \frac{2|X \cap Y|}{|X| + |Y|} \tag{1}$$

where *X* and *Y* are voxel sets taken from the most significant voxels in the original and replicated studies, respectively, and s_{xy} ranges between

0 for sets whose intersection is zero and 1 for sets that are identical (this is, sets that fully overlap). In other words, it returns the ratio of intersected voxels to the number of voxels in the evaluated set. Here, the threshold is based on the ranked significance level, and not on a predefined threshold for both sets. By considering the rank rather than one single arbitrary cutoff alpha level, we take advantage of the monotonic relationship between the distributions, compensating to some extent for SNR differences emanating from the use of different scanners and groups of participants. In the fMRI literature, the Dice coefficient has been extensively used to assess reliability generally between suprathreshold activity (Bennett & Miller, 2010; Gorgolewski et al., 2013; Ferradal et al., 2014; Wagner et al., 2005), although it has also been used with variable statistical thresholds to define active voxels and thus avoid conditioning the results by an arbitrary choice (Duncan et al., 2009). This procedure is then repeated by gradually increasing the proportion of voxels from 0.1% to 50% of the total amount of voxels, in 1000 logarithmic steps. A logarithmic scale allows a more comprehensive analysis of the proportions that contain most significant voxels. This way, an important reduction is achieved in the number of larger proportions characterized by the inclusion of the most non-significant voxels. The Dice coefficient was computed separately for positive and negative correlating voxels (hereafter referred to as negative/positive polarities) at each proportion. Thus, a Dice coefficient curve is obtained that describes the amount of overlap as a function of the proportion of total number of voxels considered in the computation of the Dice coefficient (see Fig. 2A).

Next, to assess the significance of the resulting overlaps, we computed the probability of getting an overlap equal to the one found between datasets at each of the increasing proportions of brain volume compared. To this end, permutation tests were run to derive a null distribution overlap curve as a function of proportion. For each acoustic component and predefined proportion, we created 1000 pairs of maps with similar spatial properties to the original and replicated maps being compared following the approach explained in 2.7.1. We then estimated the Dice coefficient between all pairs, and computed the mean and standard deviation across all trials as a function of proportion. Using the empirical data, we converted the overlap values per proportion to Z scores by subtracting their empirical means and then dividing by their empirical standard deviations. The resulting significance curves are shown in Fig. 2B.

3. Results

3.1. Spatial correlation of the whole brain maps (interclass correlation coefficient)

Overall, the results could be replicated with varying degrees of significance: the functional topography underlying processing of timbral features was significantly similar in both datasets (Fullness $r = .40$, $p < .005$; Brightness $r = .51$, $p < .001$; Timbral Complexity $r = .36$, $p < .01$; Activity $r = .32$, $p < .05$), whereas the functional topography associated with the processing of tonal and rhythmical features, although positively correlated, did not reach significance at the conventional alpha level (Key Clarity $r = .15$, $p = .26$; Pulse Clarity $r = .14$, $p = .29$; see Fig. 1). We reran the analysis with a larger sample including 18 musicians and the obtained coefficients were very similar, on average, only within .05 points between the original and replication maps. However, for the sake of replicability and to make the two datasets comparable in terms of their statistical power, we have adopted the same sample size as in the original study ($N = 11$), including only participants that best matched the characteristics of the original pool.

3.2. Overlap of active voxels between maps (Dice coefficient)

Compared to the interclass correlation approach, this approach is more comprehensive. As can be seen from Fig. 2B, significant overlaps can be found for most of the proportions for all acoustic components. Furthermore, replicability for some acoustic components is different depending on the polarity (i.e., negative or positive voxels). A quick look at the significance curves reveals particularly salient significance for the timbral features, all of which show a similar curve shape with peaks towards the origin (i.e., Fullness, Brightness, and Activity for the positive polarity, and Timbral Complexity, for the negative polarity), compared to the tonal and rhythmical features. This is in agreement with the replicability results obtained using the interclass correlation approach.

A deeper analysis can be done on the significance curves, in particular, by inspecting how the significance of the overlaps varies as a function of the proportion in the comparison. A prominent curve is observed for Fullness, Brightness, Activity (positive polarity) and Timbral Complexity (negative polarity), where the replicability of overlap generally increases as the proportion decreases. In other words, the replicability improves with the significance level of the intersected voxels. The curves for Pulse Clarity (positive polarity) and Key Clarity (negative polarity) are smoother in comparison, with Key Clarity tending conversely to gradually grow as the proportion increases. The local maximum of each significance curve indicates the proportion at which the overlap (Dice coefficient) is highest relative to the chance level. Finding the local maxima reveals the associated brain area of overlap with the highest degree of replicability for a particular acoustic component. For each acoustic component, we will focus only on the polarity for which the local maximum was found.

We observe highly significant maxima for Fullness, Brightness, Activity, and Timbral Complexity located at smaller proportions and Dice coefficients ranging between .35 and .56 (see Table 2). The extent of the overlap for these acoustic components is unlikely to arise by chance at the $p < .00001$ level ($Z > 54$). Replicability for these acoustic

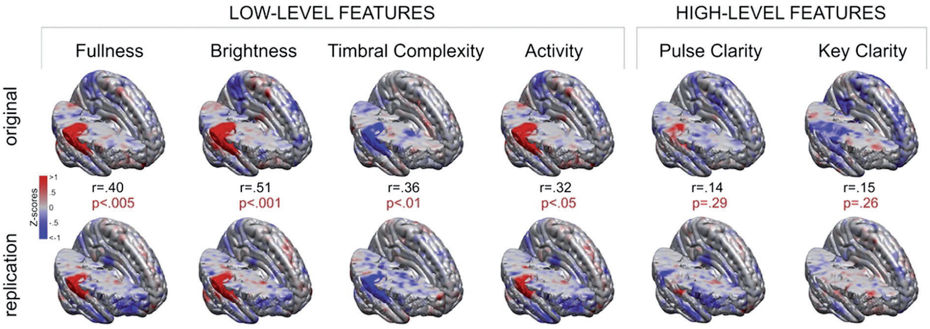

Fig. 1. Continuous Z-maps from the original and replication studies indicating the Pearson's r and p-value of the first reliability approach (interclass correlation).

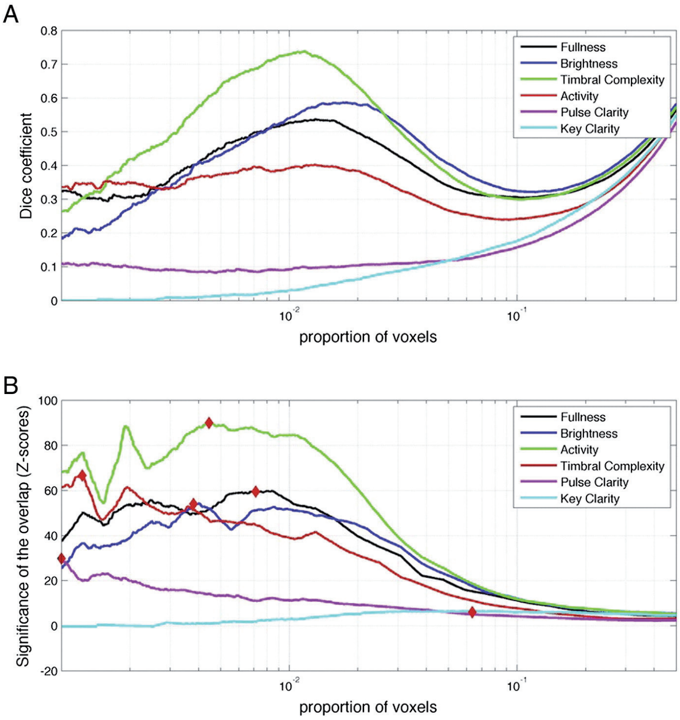

Fig. 2. (A) Curves representing the Dice coefficient as a function of proportion of most significant voxels considered for the intersection. (B) Significance curves computed from the empirical null distribution obtained via permutation tests. The local maxima are represented as red diamonds for each of the curves.

components is thus more concentrated in voxels with increased degree of activation (or deactivation, in case of the negative polarity; see Fig. 3). For Pulse Clarity the local maximum appears at the very beginning of the curve for the smallest proportion (.1%) with a Dice coefficient of .11 and at a much lower significance over chance level than for the timbral features. Finally, the significance curve for Key Clarity gradually increases yet to a much smaller extent than for the other acoustic components. A slight local maximum is observed in the curve at a larger proportion (6.38%) compared to the rest of overlaps at maximal significances. This is associated with a relatively small overlap (Dice coefficient = .14; see Fig. 3 and Table 3 for brain maps showing the overlaps and the corresponding list of regions). In short, timbral features exhibit larger Dice coefficients at their peak significant overlaps than tonal and rhythmical features. Also, significance is higher for the timbral features compared to the tonal and rhythmical ones.

Table 2
Table showing the local maxima for each of the significance curves with their associated proportion of voxels compared, and their corresponding Dice coefficient.

		Max Z	% Total voxels compared	Dice coeff.
Fullness	P	59.93	.71%	.5
Brightness	P	54.45	.38%	.4
Timbral Complexity	N	90.45	.45%	.61
Activity	P	67.18	.12%	.35
Pulse Clarity	P	30.3	.1%	.11
Key Clarity	N	6.47	6.38%	.14

Maxima are highlighted for the polarity with maximal significance. Abbreviations: Max Z = maximal Z-value, Dice coeff = Dice coefficient, P = positive polarity, N = negative polarity.

We can conclude that all timbral features plus Pulse Clarity are best replicable for the conservative thresholds, i.e., the highest activated or deactivated voxels can be replicated best. On the other hand, Key Clarity is best replicable for a slightly more liberal threshold of activation.

4. Discussion

We aimed at quantifying the replicability of previous findings on musical feature processing in the brain during naturalistic listening, by using an identical methodological approach and a similar group of participants as in the original study by Alluri et al. (2012). We computed the pairwise similarity of original and replicated musical feature maps using two measures of reliability: (1) interclass correlation, and (2) amount of overlap (Dice coefficient) at variable levels of ranked significance between the activation maps. Both approaches converge in agreement indicating a higher degree of replicability for the processing of timbral (low level) features (Fullness, Brightness, Timbral Complexity, and Activity) than for that of the tonal and rhythmical (high level) features (Key Clarity and Pulse Clarity). Neither of the reliability measures relies on comparing binary maps based on a single arbitrary cutoff p-value, but either on the whole extent of spatial activation (interclass correlation) or on various levels of ranked significance (Dice coefficient). Since the level of statistical significance can be influenced by different sources of noise dependent on the specific pool of participants, the experimental setting, and the fMRI scanner, the advantage of not relying on one single significance threshold is that this helps override to

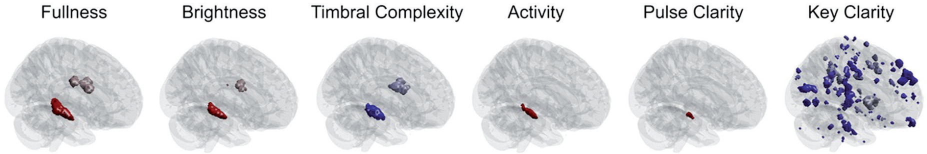

Fig 3. Maps showing the overlaps of maximal significance for each acoustic component. See Table 3 for a corresponding list of regions.

some level the possible effect of different SNR between scanners and between participants' responses at the group level.

The interclass correlation measure showed that the similarity based on the whole extent of spatial activations for each pair of maps was significant for the timbral features, while for the tonal and rhythmical features, it did not reach significance at the conventional alpha levels. Using the Dice coefficient measure allowed to identify the anatomical areas of most significant overlaps for each of the features. These are the best replicable areas for the specific features. The anatomical foci of highest reliability for all acoustic components' maps are found within the auditory cortices, except for Key Clarity, which shows a more scattered overlap (see Fig. 3 and Table 3). We observed a rightward asymmetry of the most reliable areas for Activity and Pulse Clarity within the right auditory cortex (see Fig. 3 and Table 3). In line with this, previous results attempting to assess inter-stimulus replicability using a naturalistic paradigm identified music-related activity during continuous listening as being most predictable in this right-lateralized auditory area across various musical genres (Alluri et al., 2013). This consistent finding further supports hemispheric lateralization for music processing (Toiviainen et al., 2014; Tervaniemi & Hugdahl, 2003; Riecker et al., 2002; Santosa et al., 2014).

Table 3
List of regions and their respective sizes (in number of voxels for left and right hemispheres, respectively) corresponding to the overlaps of maximal significance.

Fullness (P)	
Superior temporal gyrus (L/R)	270/448
Heschl's gyrus (R)	67
Middle temporal gyrus (L)	14
Brightness (P)	
Superior temporal gyrus (L/R)	99/224
Heschl's gyrus (R)	19
Middle temporal gyrus (L)	7
Timbral Complexity (N)	
Superior temporal gyrus (L/R)	208/353
Heschl's gyrus (R)	33
Middle temporal gyrus (L)	19
Key Clarity (N)	
Middle temporal gyrus (L/R)	346/127
Postcentral gyrus (L/R)	104/175
Superior frontal gyrus (L/R)	145/18
Superior frontal gyrus, medial (L/R)	112/45
Angular gyrus (L/R)	15/82
Precentral gyrus (L/R)	16/77
Precuneus (L/R)	40/42
Posterior cingulate and paracingulate gyrus (L/R)	45/9
Median cingulate and paracingulate gyrus (L/R)	5/47
Rolandic operculum (L/R	36/11
Middle occipital gyrus (R)	44
Gyrus rectus (L/R)	18/10
Thalamus (L/R)	7/18
Superior temporal gyrus (L/R)	5/19
Inferior frontal gyrus, triangular part (L)	21
Inferior temporal gyrus (L/R)	15/5
Middle frontal gyrus (L/R)	5/10
Parahippocampal gyrus (L)	13
Lobules IV–V of cerebellum (L)	13
Paracentral lobule (L)	14
Inferior frontal gyrus, medial orbital (R)	13
Insula (R)	9
Superior occipital gyrus (R)	11
Cuneus (L)	9
Lobule III of cerebellum (R)	7
Hippocampus (R)	7
Pulse Clarity (P)	
Superior temporal gyrus (R)	25
Activity (P)	
Superior temporal gyrus (R)	93
Heschl's gyrus (R)	5

The labels were determined using Automated Anatomical Labeling (AAL). Regions of size $<$ 5 voxels were excluded. See Fig. 3 for the corresponding maps. Abbreviations: P = positive polarity, N = negative polarity.

The second reliability approach revealed a certain degree of replicability for the two high-level features, yet to a much lesser extent (lower Dice coefficients) than for the low-level ones. In the case of Pulse Clarity, only a small set of voxels with the highest significance were best replicable. In contrast, the most reliable areas for Key Clarity are associated with below threshold activity. The fact that Key Clarity was best replicable for voxels with a slightly more liberal threshold of activation compared to the other acoustic components may reveal a property of this particular feature. What is commonly regarded as subthreshold activity has in recent times received an increased amount of attention. Assuring results from multivariate approaches (e.g., multi-voxel pattern analysis or MVPA) have found that activity that remains subthreshold in conventional univariate (general linear model) approaches is often meaningful by succeeding to recover stimulus-specific information (Riggall & Postle, 2013; Harrison & Tong, 2009; Serences et al., 2009; Sreenivasan et al., 2014; Reuter-Lorenz & Sylvester, 2005). According to this, the reliable area observed for Key Clarity (Fig. 3) may encode relevant information in scattered foci across brain areas that would have remained subthreshold in univariate analysis. Understanding the nature of this brain activity is a crucial focus for future studies.

The overall success in recruiting similar brain circuits in the processing of timbral features in two different population samples may evidence more reliable processing mechanisms for low-level acoustic features in the music compared to high-level ones. Conversely, high-level features may respond to more cognitive, top-down level mechanisms associated with larger participant-dependent variability in the BOLD responses, which may reduce replicability. A future study should aim at including individual variables as covariates to account for the person-related variability, such as individual stable traits and transient state, and test whether this inclusion alone would increase replicability. For instance, the current experimental setting comprised a longer preparation of each participant and the wearing of an electrode cap, whereas in the original study, only fMRI was measured. This setting could have caused additional discomfort (as reported by some participants in the post-experimental debriefing, affecting the transient mental state of the subject), besides contributing to additional noise during the fMRI measurements. The mental state and attention of the participants represents a potential confound for replicability within this paradigm. One way to control for attention in the future could be by using an eye tracking system during the fMRI image acquisition, since perceptual attention and memory encoding seem to be revealed by differences in eye-movement strategies (Lange & Engbert, 2013; Fischer & Breitmeyer, 1987).

Other reasons for the lower replicability in the case of the high-level features could lie in the limitations of the statistical approach used to uncover their brain correlates. Time series correlation is an isomorphic approach (Uttal, 2011) that assumes brain representations to be encoded by the same dimension used by the stimulus. However, changes in the amplitude of brain responses may not explain the variability in the measured phenomenon. An additional limitation could lie in the lack of sufficient temporal resolution of the hemodynamics that would allow a more accurate targeting of the brain correlates underlying the phenomenon. These are some of the potential drawbacks to overcome for providing both a more valid and reliable way to study these phenomena.

It is important to emphasize the inherent limitations of the fMRI experimental setup that constrain ecological validity. For instance, acoustic scanner noise may affect neural processes (e.g., increasing arousal or distraction), impacting cognitive control, and thus decreasing ecological validity (Skouras et al., 2013). However, because the scope of the study is replicability and the scanner noise was similar in the two scanning sessions, its effect across studies would be comparable. Ecological validity could be further improved with the most recent noise attenuation techniques beyond passive noise reduction and active noise cancellation, by means of a silent pulse sequence design (burst imaging, low-pass filtering gradient pulses, interleaved spiral k-imaging), by changing the MR hardware configuration, although at the cost of resolution, SNR, or motion sensitivity (Moelker & Pattynama, 2003).

In the present and original paradigm, the participants were musicians. The motivation for this selection was to avoid differences in musical expertise as a potential confounding factor. In addition, musicians exhibit larger blood oxygen level–dependent (BOLD) responses to musical sounds than nonmusicians (Pallesen et al., 2010; Brattico et al., 2013; Schneider et al., 2002; Tervaniemi, 2009), which was expected to improve SNR. It remains an open question whether musical expertise affects the reliability of results.

It is important to remark that reliability is a necessary but not sufficient condition for validity. Certain controlled paradigms that produce easily measured responses are more reliable, but often at the cost of lower ecological validity. In the words of Krippendorf (1980), reliability often gets in the way of validity. In this sense, naturalistic paradigms may inhibit reliability while increasing validity (Hasson & Honey, 2012; Hasson et al., 2010). It is therefore the best practice to design experiments that attain an appropriate balance between validity and reliability.

5. Conclusions

In conclusion, the present study supports and validates approaches of increased ecological validity over traditional paradigms in the field of cognitive neuroscience of music. At the same time, it encourages reliability assessment of fMRI studies through replication while exposing the need to carefully tune the study methodology when investigating cognitive phenomena with high inter-subject variability.

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II

ACTION IN PERCEPTION: PROMINENT VISUO-MOTOR FUNCTIONAL SYMMETRY IN MUSICIANS DURING MUSIC LISTENING

by

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RESEARCH ARTICLE

Action in Perception: Prominent Visuo-Motor Functional Symmetry in Musicians during Music Listening

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Abstract

Musical training leads to sensory and motor neuroplastic changes in the human brain. Motivated by findings on enlarged corpus callosum in musicians and asymmetric somatomotor representation in string players, we investigated the relationship between musical training, callosal anatomy, and interhemispheric functional symmetry during music listening. Functional symmetry was increased in musicians compared to nonmusicians, and in keyboardists compared to string players. This increased functional symmetry was prominent in visual and motor brain networks. Callosal size did not significantly differ between groups except for the posterior callosum in musicians compared to nonmusicians. We conclude that the distinctive postural and kinematic symmetry in instrument playing cross-modally shapes information processing in sensory-motor cortical areas during music listening. This cross-modal plasticity suggests that motor training affects music perception.

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Introduction

Within-modality neuroplasticity has been investigated extensively in the sensory and motor modalities, demonstrating the adaptive (or maladaptive [1] capabilities of the human brain to shape its processing of a sensory stimulus or to perform motor acts after repeated sensory exposure or action [2,3]). Comparing brain function and anatomy of musically trained and untrained individuals is ideal for studying neuroplasticity because of a large difference between groups in time spent with music-related activities.

Musical activities, such as playing an instrument from a musical score, involve cross-modal orchestration of auditory, visual, somatomotor, and cognitive processes [4,5]. Nevertheless, studies showing plasticity of brain function and structure associated with intensive musical

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training have thus far focused on within-modality brain measures. Early musical training has been shown to correlate with stronger auditory-cortical representations of piano vs. pure tones in pianists, supported by anatomical enlargements of the Heschl's gyrus [6,7]. The left-hand fingers of string players exhibit more extensive contralateral somatosensory cortical representations than those of nonmusicians. This effect is stronger for those string players who began musical practice at an early age [8,9]. Musicians also show more anatomical symmetry in cortical motor regions compared to controls [10]. The linking of brain anatomy and acquired sensorimotor skills is further evident in consistent within-musician differences observed in the right-left precentral gyrus depending on the instrument played [11].

These findings have led to the hypothesis that functional reorganization may cause structural adaptation [12–14]. Thus, the asymmetrical hand-motor requirements may drive the enlarged left-hand somatosensory representation in violin players. Even when limited to fifteen months in childhood [14], musical training drives an increase in grey matter for areas involved in motor, auditory, and visuo–spatial processing [15]. Similarly, an increase in cerebellar volume, presumably in response to the intensity of instrumental practice in musicians [16], suggests structural reorganization induced by long-term motor and cognitive demands derived from intense music-related auditory and motor practice. Furthermore, the size of the anterior corpus callosum (CC), which mainly connects motor areas, is enlarged in individuals with an early commencement of musical training [17,18].

The aforementioned findings motivate this study, in particular those on enlarged anterior callosum in musicians, and on enhanced somatosensory left-hand finger representation in string players. It could be assumed that morphological differences in CC are reflected in the interhemispheric functional connectivity in musicians. Several morphometric studies suggest that callosal volume predicts interhemispheric transfer capacity [19,20] and there exists evidence of a positive correlation between callosal area and the amount of fibres crossing through supporting this view [21]. However, the literature is not in agreement regarding a positive correlation between callosal size and interhemispheric transfer capacity [22–27].

Furthermore, differences in interhemispheric information transfer deriving from musical training have been only marginally investigated. While Patston and others [28] found an unusual symmetry in musicians' (mostly pianists) interhemispheric transfer speed of visual information compared to nonmusicians, previous studies have not investigated this phenomenon using musical stimulation, and have employed paradigms with controlled simple stimuli thus not allowing generalization to real life situations. Increased communication between hemispheres may extend beyond the somatosensory and motor system to other modalities that are relevant to music processing.

Here we studied the relationship between musical training, callosal volume, and interhemispheric functional symmetry in brain activity measured using functional magnetic resonance imaging (fMRI) during continuous listening to natural music. By interhemispheric functional symmetry we refer to the voxel-mirrored homotopic connectivity [29] as measured by the coactivation of homotopic (i.e., topographically matched) brain areas. Our approach consisted of three stages: (a) morphometry of participants' callosa was computed to examine a possible relationship between callosal volume and group membership; (b) symmetry indices were estimated for all voxels in the brain; and (c) significant differences between groups (musicians vs. nonmusicians and keyboard vs. string players) were assessed. We hypothesized that we would find more prominent functional symmetry in musicians, particularly in keyboard players, and particularly within motor-related brain areas. We also expected that this enhanced symmetry be accompanied by an increase in callosal volume.

Table 1. Demographic information about our sample.

group	N	age	gender	hand	soc-eco status	WAIS-III PSI	active listening (h/week)	passive listening (h/week)	total listening (h/week)
MUS	18	28.2±7.8	9F	18R	43.6	116.3	7.5±5.8	10.6±7.5	18.2±11.2
KEY	8	26.4±7	4F	8R	37.7	119.8	9.7±6.3	11.5±8.3	21.2±13.4
STR	7	28.4±7.9	5F	7R	45.3	110	5.3±1.9	10±7.3	15.3±6.1
NMUS	18	29.2 ±10.7	10F	17R	35.4	115.7	5.3±4.8	7.1±3.9	12.4±6.7

Abbreviations: MUS = musicians, KEY = keyboard players, STR = string players, NMUS = nonmusicians, class = classical, soc-eco = socioeconomic, PSI = Processing Speed Index, WMI = Working Memory Index.

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Materials and Methods

Participants

The ethics committee of the Coordinating Board of the Helsinki and Uusimaa Hospital District (Koordinoiva) approved this study with the approval number 315/13/03/00/11. Informed written consent was obtained from all participants. Consent forms are stored in a locked cabinet of NMG Data Repository. Ethics committee approved the form and the procedure. Thirty-six healthy participants with no history of neurological or psychological disorders participated in the fMRI experiment. The participants were screened for inclusion criteria before admission to the experiment (no ferromagnetic material in their body; no tattoo or recent permanent colouring; no pregnancy or breastfeeding; no chronic pharmacological medication; no claustrophobia). The participant pool was selected to be equally divided between musically trained (n = 18) and untrained participants (n = 18, left-handers = 1). The criteria for nonmusicianship was having less than 5 years of music training, not having finished a Music degree in a Music academy, not reporting themselves as musicians, and never earned money for playing. These details were obtained and crosschecked via questionnaires and HIMAB [30] (Helsinki Inventory for Music and Affect Behavior). Both groups were comparable with respect to gender, age distribution, cognitive measures (Processing Speed and Working Memory Index Scores from the WAIS-WMS III [31]), and socioeconomic status (according to Hollingshead's Four-Factor Index [32]; see Table 1 and Table 2 for demographic data). The musicians' group was homogeneous in terms of the duration of their musical training, onset age of instrument practice, and amount of years of active instrument playing.

Stimuli

Three musical pieces were used in the experiment: (a) Stream of Consciousness by Dream Theater; (b) Adios Nonino by Astor Piazzolla; and (c) Rite of Spring (comprising the first three episodes from Part I: Introduction, Augurs of Spring, and Ritual of Abduction) by Igor Stravinsky.

Table 2. Specific demographic information about musicians.

group	instrument starting age	instrument playing (years)	instrument practicing (h/week)	musical training (years)	style
MUS	8.2±4	21.2±6.2	16.6±11	15±4.7	12 class | 4 jazz | 2 pop
KEY	7±2.6	20.1±7.2	15.6±13	14.4±4	5 class | 2 jazz | 1 pop
STR	8.3±3.9	21.1±6.2	17.3±12.6	15.9±3.8	6 class | 1 jazz

Abbreviations: MUS = musicians, KEY = keyboard players, STR = string players.

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These are a progressive rock/metal piece, an Argentinian New Tango, and an iconic 20th century classical work, respectively, thus covering distinct musical genres and styles. All three selected pieces are instrumental and have a duration of about 8 minutes.

Morphometric analyses of the corpus callosum

Volumetric whole brain segmentation was performed using the FreeSurfer image analysis suite (stable Linux version 5.3.0 released on 15th of May 2013), which is available online at https://surfer.nmr.mgh.harvard.edu/. It provides completely automated parcellation of cortical and subcortical structures previously described [33–35] by assigning a neuroanatomical label to each voxel in an intensity renormalized MRI volume based on probabilistic information estimated from a manually labelled training set [33,35]. The method has been shown to be robust and comparable in accuracy to manual labelling [33,36].

The CC was segmented into five equally spaced regions of interest along the primary eigendirection as per Freesurfer's default settings (which segments the CC as a 5 mm thick slab, and divides it into 5 segments of equal length). The five regions were posterior, middle posterior, central, middle anterior, and anterior. Following this, the CC was then reorganized in two sections approximating the division used by Lee and others [18]: posterior (comprising posterior, middle posterior, and central) and anterior (comprising middle anterior and anterior). Thus the anterior CC contains interhemispheric fibres of primary somatomotor and other PFC areas, and the posterior part contains those of posterior parietal, temporal, and occipital areas [37]. Mean and standard deviation measures were extracted from posterior and anterior callosal sections.

A significant correlation was found between total callosal volume and total brain volume ($r = 0.46$, $p < 0.001$). Since the cross-sectional area of a 3D object increases as the two/thirds power of the object's volume [38], relative callosal sizes to the two/thirds power of the total brain volume were used [18].

T-tests were performed to investigate a potential relationship between participants' callosal volumes and their group membership. We hypothesized musicians' callosa to be larger than nonmusicians, and keyboardists' to be larger than string players'. To this end, two directional (right-tailed) t-tests were performed per callosal section to compare (a) musicians vs. nonmusicians, and (b) keyboardists vs. string players.

fMRI experimental procedure

Participants' brain responses were acquired while they listened to each of the musical stimuli in a counterbalanced order. For each participant the stimuli loudness was adjusted to a comfortable but audible level inside the scanner room (around 75 dB). In the scanner, participants' only task was to attentively listen to the music delivered via high-quality MR-compatible insert earphones while keeping their eyes open.

fMRI scanning and preprocessing

Scanning was performed using a 3T MAGNETOM Skyra whole-body scanner (Siemens Healthcare, Erlangen, Germany) and a standard 20-channel head-neck coil, at the Advanced Magnetic Imaging (AMI) Centre (Aalto University, Espoo, Finland). Using a single-shot gradient echo planar imaging (EPI) sequence thirty-three oblique slices (field of view = 192x192 mm; 64x64 matrix; slice thickness = 4 mm, interslice skip = 0 mm; echo time = 32 ms; flip angle = 75°) were acquired every 2 seconds, providing whole-brain coverage were imaged per participant.
T1-weighted structural images (176 slices; field of view = 256x256 mm; matrix = 256×256; slice thickness = 1 mm; interslice skip = 0 mm; pulse sequence = MPRAGE) were also collected for

individual coregistration. Functional MRI scans were preprocessed on a Matlab platform using SPM8 (Statistical Parametric Mapping), VBM5 for SPM (Voxel Based Morphometry [39]; Wellcome Department of Imaging Neuroscience, London, UK), and customized scripts developed by the present authors. For each participant, low-resolution images were realigned on six dimensions using rigid body transformations (translation and rotation corrections did not exceed 2 mm and 2° respectively), segmented into grey matter, white matter, and cerebrospinal fluid, and registered to the corresponding segmented high-resolution T1-weighted structural images. These were in turn normalized to the MNI (Montreal Neurological Institute [40]) segmented standard a priori tissue templates using a 12-parameter affine transformation. Functional images were then blurred to best accommodate anatomical and functional variations across participants as well as to enhance the signal-to-noise by means of spatial smoothing using a 8 mm full-width-at-half-maximum Gaussian filter. Movement-related variance components in fMRI time series resulting from residual motion artefacts, assessed by the six parameters of the rigid body transformation in the realignment stage were regressed out from each voxel time series. Following this, spline interpolation was used to detrend the fMRI data, followed by temporal filtering (Gaussian smoothing with kernel width = 4 sec).

Symmetrization of the brain template

Because the brain is not symmetrical (as manifested by the twisting effect, known as the Yakovlevian torque, and the right frontal and left occipital protrusions, known as petalia), homotopic voxels are not anatomically equivalent in some brain regions. To counterbalance these inherent neuroanatomical asymmetries, and make the claim for homotopic equivalency stronger, participants' brains were transformed with a spatial mapping. The goal was to create a mirror image of the continuous brain template, where voxel values represent the different intensities of the neural tissue. We thus considered the symmetrization of the brain as an unconstrained nonlinear optimization problem, aimed at minimizing a cost function—the mean squared error (MSE)—between the intensity values of the homotopic voxels of the whole brain template, as shown in Eq 1,

$$\tilde{\mathbf{a}} = \underset{\mathbf{a}}{\operatorname{argmin}} \frac{1}{V(B_L)} \int_{B_L} [b(f_{\mathbf{a}}(r(\mathbf{x}))) - b(\mathbf{x})]^2 d\mathbf{x} \qquad (1)$$

Here $\mathbf{x}$ is any position (x, y, z) in the left hemisphere space $(\mathbf{x} \in B_L)$; the function r maps the 3D coordinate point onto its homotopic counterpart $(r(\mathbf{x}) : (x, y, z) \rightarrow (-x, y, z))$; the function b returns the intensity values at the points $\mathbf{x}$; $\tilde{\mathbf{a}}$ is the optimal set of parameters for the transformation matrix f_a which maps the right hemispheric intensity values $b(r(\mathbf{x}))$ onto the left ones $b(\mathbf{x})$, so that the cost function yields the minimum error; $f_a(r(\mathbf{x}))$ is a 5th order polynomial transform. The formula is expressed as the integration of an idealized continuous 3D space. However, in reality we only know the intensity values at the grid points of the brain template, hence the other points are estimated via trilinear interpolation.

The search for the minimum was computationally expensive due to the high number of iterations and the size of the augmented matrix, which required the use of a HP super cluster (taito.csc.fi). The algorithm used for minimizing the objective function was the Nelder-Mead simplex algorithm [41].

Individuals' brains were symmetrized using the set of parameters that yielded the minimum or stationary point of the cost function. This minimum depended on the point of departure of initial conditions in the parameter space and different initial conditions do not necessarily converge to a minimizer. By randomizing the initial conditions we can reach different stationary points and chose the optimal minimizer.

The differences between the original and symmetrized brain templates were fairly minimal. This can be explained by the smoothing kernel (width = 8 mm) used in the spatial preprocessing of the fMRI data, which would override the potential asymmetries of the brain. The MSE between hemispheres of the original and transformed template were 5.7 mm^2 and 2.37 mm^2, respectively.

fMRI functional symmetry analysis

Brain responses to the three stimuli were concatenated making a total of ~24 minutes worth of data. The rationale behind this was to combine stimuli representing a wide range of musical genres and styles in order to cancel out effects that the specific kinds of music may have on the phenomenon under investigation. The final time series had 702 samples after the 4 first samples of each of the three runs were removed to avoid artefacts due to magnetization effects. Following this, symmetry indices per voxel were computed for all participants' brains. The symmetry index is the mirrored homotopic connectivity per voxel. It is obtained by correlating each voxel time series with its homotopic counterpart, i.e., correlating the brain with its own flipped image across the midsagittal plane. The results provide for each pair of homotopic voxels a measure of their degree of functional symmetry. Next, symmetry indices were transformed using Fisher's r-to-Z transformation [42] (see Eq 2) to make their sampling distribution approximately normal.

$$z_f = \operatorname{arctan}(r) \tag{2}$$

Significance had to be corrected due to the intrinsic serial correlation of the fMRI time series. To this purpose, we estimated the effective degrees of freedom of the data following a nonparametric permutation-based approach [43] as shown in Eq 3).

$$\frac{1}{df} \approx \frac{1}{N} + \frac{2}{N}\sum \frac{N-j}{N}\rho_{xx}(j)\rho_{yy}(j) \tag{3}$$

where N is the number of observations, $\rho_{xx}(j)$and $\rho_{yy}(j)$ are the autocorrelations of the pair of homotopic voxel time series at lag *j*. For each participant the effective degrees of freedom were computed by randomly selecting 1,000 pairs of homotopic voxels as the inputs x and y in Eq 3. Next, estimates from all trials across participants were averaged (mean = 110±9.6), and used to compute the significance of the symmetry index scores by dividing these by the standard error (see Eq 4).

$$z_{corrected} = z_f\sqrt{df-3} \tag{4}$$

Once whole-brain functional symmetry maps were computed and corrected for each participant, directional unpaired two-sample t-tests (alpha = 0.01, one-tailed) were performed on participants' symmetry indices in order to observe where in the brain each of the groups showed significantly greater symmetry over the other. The resulting spatial maps were corrected for multiple comparisons using the cluster-wise significance approach by Ledberg and others [44]. This is based on a Monte Carlo procedure to assess the null distribution of the cluster sizes (CS) at a particular significance level, from which the critical CS threshold can be selected.

Following Ledberg and others' method, we first computed the functional symmetry maps for all participants by correlating the brain with its own flipped and phase-scrambled image

[45]. The phase-scrambling was done in the volume domain using the 3-D Fourier transform. Once functional symmetry maps were computed, the between-groups t-test statistical map was obtained, from which an estimate of the autocorrelation function (ACF) kernel was computed.

This procedure was repeated to obtain an estimate of the ACF kernel as the average of 10 runs. This averaging decreased the amount of error and led to a more accurate ACF kernel estimate. Next, the ACF kernel was convolved with noise to generate statistical images with the same spatial spectral properties as the resulting t-test maps without containing any signal of interest. We generated 10,000 images from which we derived a probability distribution of cluster sizes above a given threshold, which was subsequently used to estimate the critical cluster size for our data. Finally, the spatial maps resulting from the t-tests were cleaned to retain clusters with a cluster size probability $p < 0.001$ (critical cluster size > 55 voxels).

At this point the resulting spatial maps showed the brain areas that are significantly more symmetrical for one group over the other (i.e., musicians > nonmusicians, nonmusicians > musicians, keyboardists > string players, and string players > keyboardists). Still, the mean symmetry index for a given voxel in group 1 may not be significantly different from zero, even though it may be significantly different from group 2. To ensure that only significantly functional symmetry is retained, t-test spatial maps were further masked with the functional symmetry averaged Fisher Z-map of the group favoured in the right-tailed t-tests at a significant level $p < 0.0005$ (right-tailed). Thus pairs of homotopic voxels whose symmetry indices did not reach significance were discarded.

Anatomical labelling was based on the Automated Anatomical Labelling (AAL [46]) implemented in the MarsBaR toolbox v0.43 (http://marsbar.sourceforge.net) and thus anatomical regions within each cluster were determined. Regions of interest were visually inspected using the MNI structural atlas and the Harvard-Oxford cortical and subcortical atlases implemented in FSL to ensure that the automatic assignment was conforming to the neurological knowledge. The x y z coordinates (in MNI space) of the maximum voxel Z-value within each anatomical region were retrieved and accordingly labelled.

Results

Morphometric analysis of the corpus callosum

T-tests results comparing relative CC volume to total brain volume were nonsignificant except for a larger posterior CC in musicians compared to nonmusicians ($p = 0.05$, one-tailed, 7.3% difference between group means; for details on the analysis see Materials and Methods).

Functional symmetry

Measures of interhemispheric functional symmetry were obtained by correlating each participant's fMRI brain responses to music at every voxel with their hemispheric counterparts. This indicates how similar the time courses are for each pair of topographically matched voxels.

Musicians vs. nonmusicians. Musicians showed significantly more symmetrical responses to music listening (brain volume = 21.42 cm^3; brain volumes here refer to the amount of significant voxels, expressed in cm^3, resulting from the t-test) than nonmusicians (brain volume = 0 cm^3; one-tailed t-test, $p < 0.01$; see Fig 1 and Table 3 for a list of regions). The symmetry was evident over a widely distributed brain area, including somatomotor regions (paracentral lobule and pre- and postcentral gyri), occipitoparietal lobe (calcarine fissure, precuneus), temporal areas (inferior/superior temporal gyrus [ITG, STG]), prefrontal cortical (PFC) areas (orbitofrontal cortex [OFC]), cerebellum (lobules VI-VIII-VIIIB-IX, Crus II), temporal regions (inferior temporal gyrus [ITG], fusiform gyrus), and a small area in the median cingulate gyrus. Nonmusicians did not exhibit more symmetrical brain responses in any areas than musicians

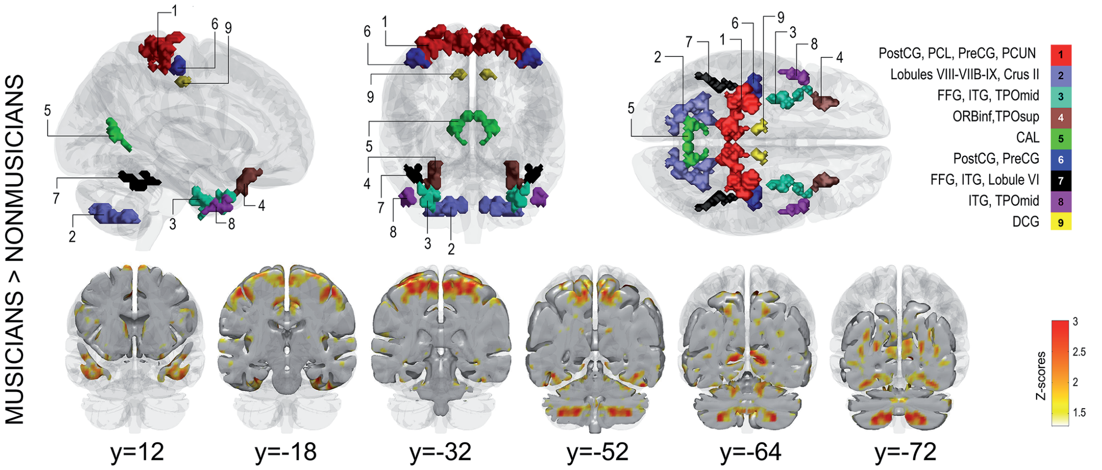

Fig 1. Symmetry maps showing significantly greater functional symmetry for musicians compared to nonmusicians. Top of figure: Orthogonal planes (lateral, frontal, transversal) showing significant clusters (voxelwise thresholded at $p < 0.01$ [$z = 2.32$]; cluster-wise corrected at $p < 0.001$). Bottom of figure: Coronal slices showing the continuous Z-map for the respective comparison. Abbreviations: PostCG = postcentral gyrus, PCL = paracentral lobule, PreCG = precentral gyrus, PCUN = precuneus, FFG = fusiform gyrus, ITG = inferior temporal gyrus, TPOmid = temporal pole (middle temporal gyrus), ORBinf = orbitofrontal cortex (inferior frontal gyrus), TPOsup = temporal pole (superior temporal gyrus), CAL = calcarine fissure and surrounding cortex, DCG = median cingulate and paracingulate gyrus.

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at the chosen significance level. Effect sizes were computed for all voxels. Large effect sizes were found more extensively for musicians (Cohen's $d > 0.8 = 39.26$ cm^3 brain volume) than for nonmusicians (Cohen's $d > 0.8 = 2.82$ cm^3 brain volume).

Keyboard vs. string players. Keyboardists showed more prominent symmetrical responses to music listening (brain volume = 10.37 cm^3) than string players (brain volume = 0.90 cm^3; one-tailed t-test, $p < 0.01$; see Fig 2 [top figure] and Table 4 for a list of regions). Keyboardists' brain responses were predominantly symmetrical in regions within the occipital and parietal lobes (middle and superior occipital gyrus [MOG, SOG], cuneus, precuneus, superior parietal gyrus ([SPG]), somatosensory cortex (postcentral gyrus), temporal areas (fusiform gyrus), cerebellum (lobules IV-V-VI), and a small subcortical area within the dorsal striatum (caudate nucleus and putamen). For the string players, however, only one small cluster in the middle frontal gyrus (MFG) and SFG displayed more prominent symmetry over the keyboardists (see Fig 2 [bottom figure] and Table 5 for a list of regions). Effect sizes revealed a greater brain volume showing large effect sizes for the keyboardists (Cohen's $d > 0.8 = 184.61$ cm^3) than for the string players (Cohen's $d > 0.8 = 49.31$ cm^3).

Discussion

Morphometric analysis of the corpus callosum

When comparing posterior and anterior callosal measures in musicians vs. nonmusicians, and in keyboard vs. string players, only musicians' posterior callosa were significantly larger compared to those of nonmusicians. Lee and others [18] found a similar effect between musicians and nonmusicians in their morphometric study. However, they found a significant difference in the anterior section of the callosum, while a near-significant trend was observed in the

Table 3. Functional symmetry results for musicians.

MUSICIANS	k	max Z	x	y	z	BA
Cluster 1						
Postcentral gyrus	217	3.39	-18	-36	68	4
Paracentral lobule	99	3.55	-8	-36	70	4
Precentral gyrus	97	3.13	-30	-24	74	4
Precuneus	79	3.40	-16	-38	68	4
Cluster 2						
Lobule VIII of cerebellum	153	3.49	-28	-64	-48	-
Lobule VIIB of cerebellum	82	3.56	-20	-70	-42	-
Lobule IX of cerebellum	29	3.12	-16	-48	-50	-
Crus II of cerebellum	12	3.24	-24	-74	-46	-
Cluster 3						
Fusiform gyrus	54	3.05	-28	0	-38	36
Inferior temporal gyrus	39	3.01	-34	-2	-36	36
Temporal pole, middle temporal gyrus	32	2.80	-40	14	-32	38
Cluster 4						
Inferior frontal gyrus, orbital part	69	3.54	-30	26	-18	47
Temporal pole, superior temporal gyrus	24	3.08	-28	24	-30	38
Cluster 5						
Calcarine fissure and surrounding cortex	76	3.37	-14	-64	8	17
Cluster 6						
Postcentral gyrus	54	3.18	-46	-22	54	3
Precentral gyrus	26	2.80	-42	-20	58	4
Cluster 7						
Fusiform gyrus	38	3.56	-44	-50	-24	37
Inferior temporal gyrus	28	3.08	-40	-44	-18	37
Lobule VI of cerebellum	8	2.83	-40	-46	-28	37
Cluster 8						
Inferior temporal gyrus	31	2.96	-52	4	-40	20
Temporal pole, middle temporal gyrus	12	2.76	-48	12	-36	20
Cluster 9						
Median cingulate and paracingulate gyrus	25	2.98	-10	-20	44	-

Brain areas showing significantly greater functional symmetry for musicians compared to nonmusicians. Nonmusicians did not show greater symmetry than musicians. Clusters were obtained via the 18-connectivity scheme employed in SPM. The table reports within-cluster region size (k; i.e., number of voxels), peak Z-statistic value per region within the cluster, and its respective MNI coordinates and Brodmann area (BA). Labels here correspond to the left-hemisphere. Voxels identified as white matter or voxels encroaching very small regions within the cluster (k< 5 voxels) were discarded from the resulting table.

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posterior section. Additional correlational analyses were performed between callosal volumes and symmetry indices. However, they did not yield any significant results.

Although there exists evidence linking increased callosal volume, number of fibres crossing through the callosum, and enhanced interhemispheric connectivity [19–21] which suggests that callosal size is a good a marker of information transfer between hemispheres, there does not seem to be a consensus in the literature on a strict correlation between callosal size and the efficiency of interhemispheric transfer, which obscures this relationship [22].

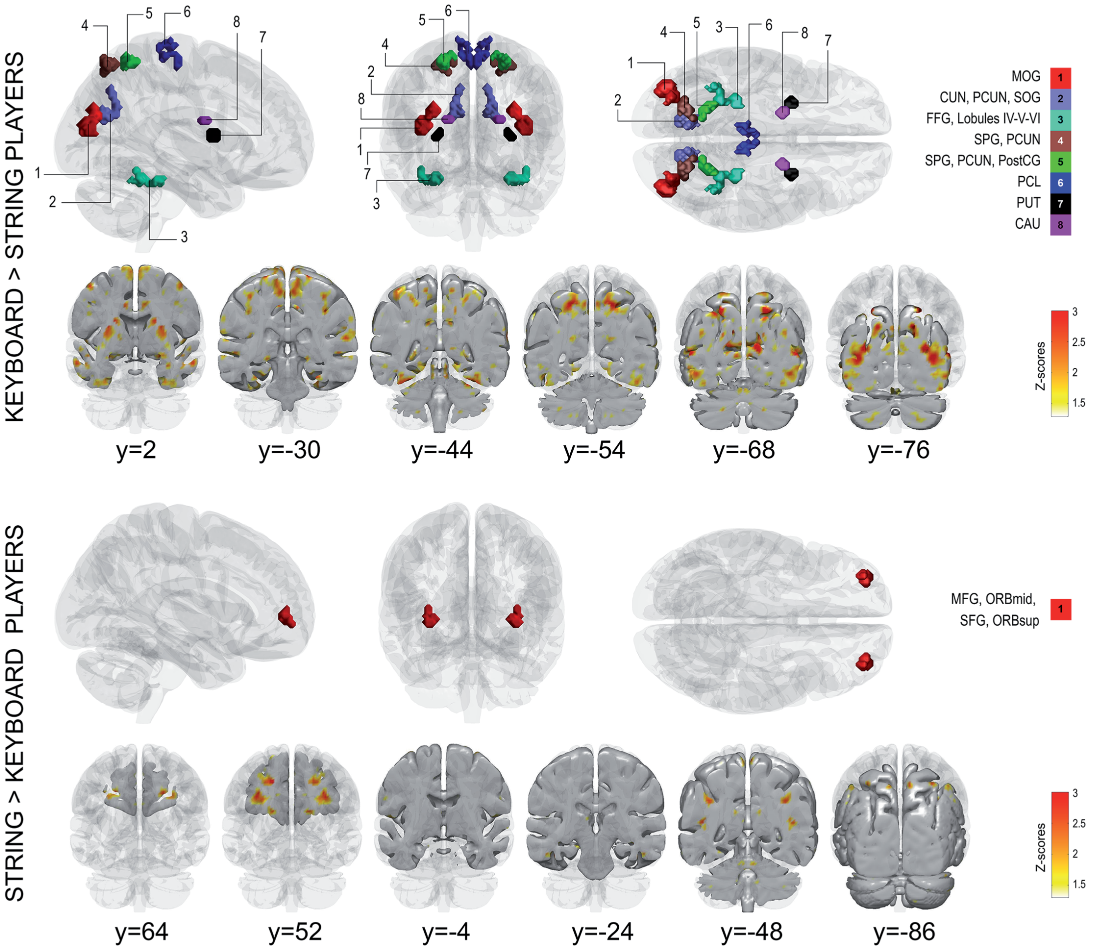

Fig 2. Symmetry maps showing significantly greater functional symmetry for keyboard players compared to string players (top figure) and for string players compared to keyboard players (bottom figure). See legend of Fig 1 for further details. Abbreviations: MOG = middle occipital gyrus, CUN = cuneus, PCUN = Precuneus, SOG, superior occipital gyrus, FFG = fusiform gyrus, SPG = superior parietal gyrus, PostCG = postcentral gyrus, PCL = paracentral lobule, PUT = putamen, CAU = caudate nucleus, MFG = middle frontal gyrus, ORBmid = orbitofrontal cortex (middle frontal gyrus), SFG = superior frontal gyrus, ORBsup = orbitofrontal cortex (superior frontal gyrus).

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Furthermore, interhemispheric functional connectivity can be widely preserved following callosal agenesis [23] or surgical lesions of the callosum [24–27]. Thus, decreased structural connectivity is not necessarily associated with decreased functional connectivity [25].

Although callosal structure comprises several independently functioning components that under some conditions may produce contralateral inhibition [47], it is widely assumed that the role of the corpus callosum is excitatory. However, the callosum may be a channel for both interhemispheric excitation and inhibition [47]. It is a task for future research to investigate the

Table 4. Functional symmetry results for keyboard players.

KEYBOARD PLAYERS	k	max Z	x	y	z	BA
Cluster 1						
Middle occipital gyrus	170	4.55	-36	-84	14	19
Cluster 2						
Cuneus	65	3.76	-14	-70	22	-
Precuneus	26	3.87	-10	-66	40	7
Superior occipital gyrus	10	3.47	-16	-72	22	18
Cluster 3						
Fusiform gyrus	84	3.33	-30	-46	-22	37
Lobule VI of cerebellum	5	3.30	-28	-46	-22	37
Lobules IV-V of cerebellum	5	2.56	-26	-46	-22	37
Cluster 4						
Superior parietal gyrus	83	4.30	-24	-70	58	7
Precuneus	6	3.65	-14	-64	58	7
Cluster 5						
Superior parietal gyrus	50	3.62	-20	-56	60	5
Precuneus	7	2.66	-16	-58	62	5
Postcentral gyrus	5	3.22	-22	-52	58	5
Cluster 6						
Paracentral lobule	59	2.83	-6	-32	62	4
Cluster 7						
Putamen	34	3.55	-28	2	8	48
Cluster 8						
Caudate nucleus	12	2.82	-20	0	20	-

Brain areas showing significantly greater functional symmetry for keyboard players compared to string players (see legend of Table 3 for further details).

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callosal structures in detail using appropriate methods to better characterize callosal fibres in combination with interhemispheric functional measures [48].

The present non-conclusive result of the morphological analyses of the callosum exposes the lack of agreement in previous neuroimaging results regarding the relationship between callosal size and interhemispheric transfer.

Functional symmetry

Musicians vs. nonmusicians. The increased functional symmetry in musicians, mainly observed in brain regions involved in somatosensory and motor control in the parietal and

Table 5. Functional symmetry results for string players.

STRING PLAYERS	k	max Z	x	y	z	BA
Cluster 1						
Middle frontal gyrus	27	2.96	-32	50	6	10
Middle frontal gyrus, orbital part	10	2.78	-32	54	-4	47
Superior frontal gyrus	10	3.28	-30	52	0	11
Superior frontal gyrus, orbital part	9	3.12	-30	54	-2	11

Brain areas showing significantly greater functional symmetry for string players compared to keyboard players (see legend of Table 3 for further details).

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frontal lobes, is in agreement with the specific motor demands of musicianship. Instrument practice has been shown to enhance motor ability as measured by finger dexterity in both hands [14]. Also the prominent symmetry observed in musicians' cerebellar responses conforms to the specific motor demands of musicianship. The cerebellum is central to motor programming and learning and therefore play a crucial role in developing musical skills [49]. The intensity of musical training manifests in cerebellar morphology, where cerebellar volume and lifelong intensity of practice correlate positively [16].

Rather than being confined only to motor and perceptual processes, the demands of musicianship are complex and multimodal, supported by several skills developed during years of study [50]. These include bottom-up skills such as the ability to perceive and distinguish the physical properties of music, and top-down skills such as the ability to predict musical events based on prior musical exposure. Instrument practice seems to enhance auditory melodic and rhythmic discrimination [14]. For instance, musicians react faster than nonmusicians to sound stream presentation, especially to sounds consisting of familiar timbres [51,52], but also to slight mistunings [53], indicating superior attentive auditory discrimination skills for musically trained individuals. They also show a mismatch negativity (MMN) for tones mistimed by only 20 ms compared to nonmusicians [54]. Furthermore, when playing in an ensemble, ensuring tight coordination and prompt responses to several sensory stimuli in the interaction with other team members is crucial for a successful joint performance. Such expert skills may require the symmetric use of both hemispheres for speed and efficiency (e.g., in multimodal integration), reflecting greater functional connectivity between homotopic brain areas. Previous research has revealed a more balanced attentional capacity and faster choice reaction times in musicians, as well as enhanced visuomotor ability, when compared to nonmusicians [55], which was attributed by the authors to the cognitive demands of playing a bimanual instrument from childhood.

We also observed symmetric brain responses in musicians' fronto-parietal areas belonging to the human mirror neuron system [56]. Listening to music may have hence activated neurons that also govern the motor production of those sounds, extending findings obtained in studies on music listening [57]. We speculate that musical training would shape the symmetry of the brain responses mainly in fronto-parietal regions due to its coupling between production and perception of music. One question that arises is whether the symmetrical motor activity is in response to the music. It is known that the motor system is active in response to music listening [58], and displays significant mean inter-subject correlation bilaterally [59], suggesting that the bilateral motor responses are likely to be stimulus-driven.

Keyboard vs. string players. The enhanced somatomotor functional symmetry of the keyboard players over the string players may be understood as a result of a more mirrored use of both hands and fingers in keyboardists than in string players. Furthermore, keyboardists had enhanced functional symmetry in subcortical brain responses from the dorsal striatum (comprising caudate nucleus and putamen). This striatal area is an important hub, receiving input from sensorimotor and association cortices. One of its functions is to mediate inhibition of voluntary fine-motor movements when required [60], and in holding back prepared motor responses [61]. Thus, the different symmetry in keyboard and string players reflects specific competences required for mastering each instrument: a midline, symmetrically bimanual instrument like the piano [28] where exact motor timing for synchronization of both hands is required [62], as opposed to a mediolateral, asymmetrically bimanual instrument like the violin, in which arms, hands and fingers play a different role when performing, namely, the right hand controls the movement of the bow while the left hand is concerned with fingering the strings, and where the coordination between fingering and bowing is not synchronous [63]. Thus, although playing a string instrument also requires fine motor skills and bimanual hand coordination, it enforces a strict asynchrony between finger movements (placing fingers on the board) and the up and down bowing. This guides the differences between string players and keyboardists, who instead need absolute synchrony between hands to achieve flawless performance.

The prominent symmetry largely focalized in the visual areas in keyboardists compared to string players may arise from the need to acquire visual information (i.e., score reading) for both right and left hands, while simultaneously monitoring the synchronized movements of both hands. Piano playing from a score is a complex transcription task with high-visual-load activity that involves active, continuous, multiple-part reading of parallel sequences of events. This requires efficient visual scanning strategies [64]. In contrast, score reading for string players is for the most part a serial process, that is, the reading of one melody line at a time. The implications of these unequal visual-processing requirements may have an impact on the interhemispheric synchrony and speed of the visual responses, which, in turn, would affect the degree of functional symmetry in the implicated areas, as observed in the present study. The observed functional symmetry in visual areas in musicians (specifically keyboardists) is in agreement with work by Patson and others [28]. They observed an unusual lack of asymmetry in the interhemispheric transfer time and latency of the visual responses of musicians vs. nonmusicians. In other words, their results indicated a more balanced visual processing in musicians than in nonmusicians. Since in their study most of the musicians played a midline, bimanual instrument (i.e., piano or clarinet), they hypothesized that the cognitive demands of such instruments, and particularly the transfer of visual inputs from musical scores to bilateral motor outputs, may produce equilateral neural connectivity and myelination in both hemispheres, advantageous for speed and accuracy in musical performance. Our additional finding of significantly stronger symmetry of string vs. keyboard players in the MFG/SFG is a novel one and calls for further study.

These results are meaningful in the light of a recent study by Vollman and others [65] which evidenced how different instrument training regimes may result in different structure-function relationships. They observed that string players exhibited a significant positive relationship between fractional anisotropy, a measure of white matter organization, in the posterior midbody of the corpus callosum, and interhemispheric inhibition (IHI), as examined by transcranial magnetic stimulation. Interestingly, this relationship was not significant in pianists or in non-expert controls. The microstructural white matter architecture of the corpus callosum was thus assessed as a marker for interhemispheric information processing within the motor system, replicating previous results in the literature, namely, that microstructural information of the hand callosal motor fibres significantly correlates with functional connectivity measures of IHI between the primary motor cortical hand areas in both hemispheres [66]. These findings indicate the existence of a link between the mode of bimanual training (piano vs. string players), neurophysiology and brain anatomy, as seen in the white-matter structure in the corpus callosum. Consequently, the characterization of the white matter tracts, rather than the size of the corpus callosum, may better reflect a correlation with interhemispheric functional connectivity measures.

Increased transfer of information across hemispheres does not necessarily result in enhanced functional symmetry, unless it happens between anatomically equivalent areas. Thus the condition of homotopicity needs to be satisfied. Functional brain asymmetries as a result of violin practice (e.g., left-hand finger motor specialization [8]) render homotopic brain regions not anatomically or functionally equivalent. This would explain why string players showed significantly less symmetry than keyboardists in motor areas. Thus practice-dependent brain plasticity seems to be a potential factor in the emergence of different symmetry patterns between groups.

The increased symmetric responses in motor and visual areas in musicians, particularly in keyboard players, are assumed to derive from the intensive practice of symmetrical bimanual movements and multipart reading. This would support the premise that functional symmetry results from interhemispheric (thus transcallosal), rather than intrahemispheric, integration. Thus, although functional symmetry could result from strengthened auditory-motor ipsilateral connectivity, our results suggest that it occurs via contralateral connectivity. Moreover, there seems to exists a consensus about the existence of training-induced plasticity in cross-hemispheric connections in musicians, whereas findings on differences in intra-hemispheric fibres between musically trained and untrained individuals have not always been replicated [67].

In view of our present findings on functional symmetry, distinctive kinematics and posture of performing the instrument seem to be crucial factors in shaping the symmetry, although the direction of the effect cannot be inferred from the data. Nonetheless, several studies have found that long-term and intensive musical training may enhance the ability to integrate input from several sensory modalities [14,15,68], which in turn, we hypothesize, may increase the degree of functional symmetry between hemispheres for specific modalities.

Limitations. Our study does not directly assess whether increased symmetry is produced by musical training. Previous research has established a positive correlation between brain function, morphology, and early commencement of musical training [6–8,10,15–18,69]. However, whether it is an innate neuroarchitecture that induces functional plasticity predisposing children to thrive musically, or whether the differential neuroarchitecture is an effect of the functional requirements of a life-long, intensive musical training, has to date not been established with a longitudinal study. Many significant aspects seem to influence children's musical instrument choices, such as sociocultural influences, gender stereotyping, instrument size or timbre, and instrument availability and cost [70]. Thus, although preselectional bias cannot be completely ruled out, functional symmetry differences between keyboard and string players would seem to arise as a result of adaptation to intensive musical training rather than as result of an intrinsic early predisposition [71].

Another limitation of the study is the lack of a behavioral task to support the claim of a cross-modal transfer effect, given that musical training comprises both listening and performing. We argue that the listening side of the musical training is unavoidably influenced or coupled by the motor training resulting from playing an instrument, and this would manifest in the brain responses to music listening alone.

Similarly, one could argue that musicians demonstrated a higher degree of coupling in bilateral motor areas because they were performing motor imagery when listening (i.e. imagining themselves playing the piece), and hence the same could have been potentially true for nonmusicians had they been asked to perform motor imagery. However, if the musical training is driving the coupling of the perceptual-motor system, one could speculate that the degree of homotopic connectivity would be weaker in musically untrained individuals, even if they are asked to perform motor imagery during the listening. These hypothesis-generating results provide a foundation for future studies.

Conclusion

We show here functional symmetry differences during music listening between musicians and nonmusicians, in addition to functional symmetry profiles for different kinds of musicians [49], thereby demonstrating a dependency between musical training and functional symmetry. Our results indicate a cross-modal transfer effect between musical training and music perception: symmetrical actions derived from musical training manifest in symmetrical brain responses while listening to music. The observed cross-modal transfer of symmetry from sensorimotor to perceptual processing systems suggests that motor training affects music perception. This finding has major implications for a better understanding of cross-modal neuroplasticity, in other words, changes in neural processing in one modality driven by experience or training in another modality [2], an area of increasing interest in neuroscience [50], which investigates the ability of the brain to reconfigure itself to create alternate neural pathways.

Supporting Information

S1 Information. Navigable 3D volume corresponding to Fig 1. Brain areas showing increased functional symmetry in musicians compared to nonmusicians).
(NII)

S2 Information. Navigable 3D volume corresponding to top of Fig 2. Brain areas showing increased functional symmetry in keyboard players compared to string players).
(NII)

S3 Information. Navigable 3D volume corresponding to bottom of Fig 2. Brain areas showing increased functional symmetry in string players compared to keyboard players).
(NII)

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Author Contributions

Conceived and designed the experiments: IB PT. Performed the experiments: EB. Analyzed the data: IB PT EB TP MS TR. Contributed reagents/materials/analysis tools: IB PT EB TP. Wrote the paper: IB PT EB TP MS TR.

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III

MUSIC TRAINING PREDICTS CEREBELLO-HIPPOCAMPAL COUPLING DURING MUSIC LISTENING

by

Iballa Burunat, Martin Hartmann, Elvira Brattico, Peter Vuust, &
Petri Toiviainen (preprint; under review)

IV

COUPLING OF ACTION-PERCEPTION BRAIN NETWORKS DURING RHYTHM PROCESSING: EVIDENCE FROM REGION-OF-INTEREST-BASED INDEPENDENT COMPONENT ANALYSIS

by

Iballa Burunat, Valeri Tsatsishvili, Elvira Brattico, & Petri Toiviainen
(preprint; under review)