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Experience-dependent plasticity in the auditory domain: effects of expertise and training on functional brain organization

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Declaration of authorship / Eidesstattliche Erklärung

I hereby declare in lieu of oath that I have written this dissertation independently and without unauthorized assistance, that I have not submitted this dissertation to any other university and that I do not hold a doctorate degree in the subject of psychology, that contributions by other authors have been acknowledged and that I am aware of the doctoral regulations for the degree if Dr. rer. nat/Ph. D. in the Department of Education and Psychology at the Freie Universität Berlin dated August 8th, 2016 (35/2016).

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und ohne unerlaubte Hilfe verfasst habe, dass ich die Dissertation an keiner anderen Universität eingereicht habe und keinen Doktorgrad in dem Promotionsfact Psychologie besitze, dass die die Beiträge anderer Autoren anerkannt wurden und dass mir die Promotionsordnung zum Dr. rer. nat/Ph. D des Fachbereichs Erziehungswissenschaft und Psychologie der Freien Universität Berlin vom 8. August 2016 (25/2016) bekannt ist.

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Eleftheria Papadaki

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Summary

In the definition this dissertation adheres to, brain plasticity denotes the brain's capacity to undergo adaptive changes in its structure and function in response to demands posed externally, in contexts of learning and skill acquisition. From early on, musicians have been a favored group in studying the effects of intensive training on the brain's structure and function, using Magnetic Resonance Imaging (MRI). The yearlong intensive training musicians undergo puts great demands not only on sensory and motor systems and their integration, but also on higher-order cognitive processing systems. Conceptual and methodological enrichment from the field of network neuroscience have offered a view of the brain as a complex system of interacting elements. According to this view, plastic changes occurring with training and facilitating expertise-like behavior can be associated with changes in functional networks' properties and aspects of network organization.

In this context, the present dissertation aims at systematically investigating manifestations of experience-dependent plasticity in the auditory domain, resulting from intensive musical training, utilizing analytical tools from network neuroscience. The dissertation is based on data acquired in the course of a longitudinal study investigating structural and functional changes in the auditory domain due to music training. A group of aspiring professional musicians, attending preparatory courses for entrance exams at universities of arts, and a group of amateur musicians, actively practicing in their everyday life, completed up to 5 behavioral and neuroimaging assessments in the course of one year. The dissertation consists of three studies addressing cross-sectional and longitudinal aspects of functional plastic differences and changes, respectively, ranging from a specific auditory process over unconstrained music listening to longitudinal changes in functional organization.

In the first study, I examined differences in the functional organization of a network of brain regions facilitating interval recognition, between the group of aspiring professional musicians and amateur ones. Aspiring professionals had overall higher connectivity and global efficiency, a graph measure of information transmission efficacy, among the network regions. In addition, these metrics correlated with performance in separately assessed tests of interval identification. In the second study, I examined whole-brain connectivity configurations during listening to two music pieces, examining how these configurations reflect different processing demands and how they are expressed in the two groups that differ in expertise. Listening to the piece posing higher processing demands was related for all participants with a more integrated

and interconnected network configuration, reflecting the brain's adaptation to processing demands. In addition, the group of aspiring professional musicians exhibited higher global efficiency in the more challenging listening condition and flexibly utilized music-related processing brain regions, in response to the demands of each listening condition. In the third study, I assessed the effects of music training longitudinally, examining the functional changes occurring over time in a core region of auditory processing, the left planum polare. While this region was undergoing reductions in grey matter volume, its functional connectivity to other musically relevant regions increased. This increase in connectivity was also reflected in network metrics of local and global integration.

Overall, with these three studies, I aimed to uncover effects of musical training and expertise in functional organization, using connectivity measures and analytical tools from network neuroscience. In addition, I aimed to examine changes in functional organization over time taking place in parallel with changes in grey matter morphology. I conclude that the joint examination of functional and structural changes in the course of skill acquisition can lead to a better and more nuanced understanding of human brain plasticity.

Zusammenfassung

Gemäß der in der vorliegenden Dissertation verwandten Definition bezeichnet Plastizität des Gehirns die Eigenschaft des Gehirns, seine Struktur und Funktion als Reaktion auf externe Anforderungen im Zusammenhang mit dem Erwerb von Fertigkeiten zu verändern. Musiker waren schon früh eine bevorzugte Gruppe bei der Untersuchung der Auswirkungen des Fertigkeitserwerbs auf die Struktur und Funktion des Gehirns mit Hilfe der Magnetresonanztomographie (MRT). Das jahrelange intensive Training, dem sich Musiker unterziehen, stellt hohe Anforderungen nicht nur an die sensorischen und motorischen Systeme und deren Integration, sondern auch an kognitive Verarbeitungssysteme höherer Ordnung. Begriffliche und methodologische Entwicklungen der Netzwerk-Neurowissenschaften haben ein besseres Verständnis des Gehirns als komplexes System interagierender Elemente ermöglicht. Demnach sind plastische Veränderungen, die durch Training hervorgerufen werden und Verhalten auf Expertenniveau ermöglichen, mit Veränderungen in der Netzwerkorganisation assoziiert.

In Rahmen dieser Überlegungen zielt diese Dissertation darauf ab, Manifestationen erfahrungsabhängiger Plastizität im auditorischen Bereich, die sich aus intensivem Musiktraining ergeben, mit Hilfe der Nutzung analytischer Werkzeuge der Netzwerk-Neurowissenschaften systematisch zu untersuchen. Die Dissertation basiert auf Daten, die im Rahmen einer Studie gewonnen wurden, in der trainingsbedingte strukturelle und funktionelle Veränderungen im auditorischen Bereich untersucht wurden. Eine Gruppe von angehenden Berufsmusikern, die an Vorbereitungskursen für Aufnahmeprüfungen an Kunsthochschulen teilnahmen, und eine Gruppe von Amateurmusikern, die aktiv in ihrem Alltag übten, absolvierten im Laufe eines Jahres bis zu fünf Verhaltens- und MRT-Untersuchungen. Die Dissertation besteht aus drei Projekten, die sich mit Querschnitts- und Längsschnittaspekten funktioneller plastischer Unterschiede und Veränderungen befassen, ausgehend vom experimentell stark kontrollierten Kontext eines spezifischen Hörprozesses über freies Musikhören bis hin zu längsschnittlichen Veränderungen in der funktionellen Organisation.

Im ersten Projekt untersuchte ich die Unterschiede zwischen einer Gruppe von angehenden Berufsmusikern und Amateurmusikern in der funktionellen Organisation eines Netzwerks von Hirnregionen, die die Intervallerkennung erleichtern. Die angehenden Profimusiker wiesen insgesamt ein höheres Ausmaß an Konnektivität und globaler Effizienz auf; letztere gilt als Maß für der Übertragungseffizienz zwischen Netzwerkregionen. Beide Maße korrelierten mit der Leistung in separat erfassten Tests der Intervallidentifikation. Im zweiten Projekt untersuchte ich die Konnektivitätskonfigurationen weiter Teile des Gehirns

während des Hörens von zwei Musikstücken. Ich nahm an, dass die beiden Stücke verschiedene Höranforderungen stellen, die mit dem unterschiedlichen Fachwissen der beiden Gruppen interagieren sollten. Das Anhören des vermeintlich verarbeitungsintensiveren Stücks war bei allen Teilnehmern mit einer stärker integrierten und vernetzten Konnektivitätskonfiguration verbunden, die als Anpassung des Gehirns an erhöhte Verarbeitungsanforderungen gedeutet werden kann. Darüber hinaus zeigte die Gruppe der angehenden Berufsmusiker in der anspruchsvolleren Hörbedingung eine höhere globale Effizienz und nutzte musikbezogene Hirnregionen in Abhängigkeit von den Anforderungen der jeweiligen Hörbedingung. Im dritten Projekt untersuchte ich längsschnittlich die funktionellen und strukturellen Auswirkungen des Musiktrainings auf das linke *planum polare*, einer Kernregion der Hörverarbeitung. Während sich das Volumen der grauen Substanz in dieser Region verringerte, nahm die funktionelle Konnektivität zu anderen musikalisch relevanten Regionen zu. Dieser Anstieg der Konnektivität spiegelte sich auch in den Netzwerkmetriken der lokalen und globalen Integration wider.

Das forschungsleitende Ziel meiner Dissertation bestand darin, die Auswirkungen von musikalischem Training und musikalischer Expertise auf die funktionelle Organisation des Gehirns näher zu untersuchen. Hierzu nutzte ich Konnektivitätsmaße und Analysewerkzeuge der Netzwerkneurowissenschaften. Darüber hinaus identifizierte ich trainingsinduzierte längsschnittliche Veränderungen in der funktionellen Organisation musikrelevanter Teile des Gehirns, die gemeinsam mit Veränderungen in der Morphologie der grauen Substanz auftraten. Die Ergebnisse meiner Dissertation belegen den wissenschaftlichen Ertrag der gemeinsamen Untersuchung funktioneller und struktureller Korrelate des Fertigkeitserwerbs für das Verständnis der Plastizität des menschlichen Gehirns.

List of original papers

1. Papadaki E., Koustakas T., Werner A., Lindenberger U., Kühn S., Wenger E., Resting state functional connectivity in an auditory network differs between aspiring professional and amateur musicians and correlates with performance. *under review in Brain Structure and Function since January 2023.*

2. Papadaki E., Lin Z., Werner A., Brandmaier A.M., Lindenberger U., Kühn S., Wenger E., Comparing the neural correlates of experiencing music by J.S. Bach and A. Webern: Music expertise matters in contemporary classical music. *in preparation for submission.*

3. Wenger E., Papadaki E., Werner A., Kühn S., Lindenberger U., Observing Plasticity of the Auditory System: Volumetric Decreases Along with Increased Functional Connectivity in Aspiring Professional Musicians, *Cerebral Cortex Communications*, Volume 2, Issue 2, 2021, tgab008, https://doi.org/10.1093/texcom/tgab008

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1 Introductory remarks on brain plasticity

The term brain plasticity vaguely denoting any sort of alterations on the neural level associated with behavioral modifications, as a result of development, maturation, learning, or compensatory processes, has a long history spanning more than a century[1]. In the approximately 150 years of the use of the term with this meaning, it has been linked with numerous scientific findings and scientists, witch its content being progressively enriched and specialized. An exhaustive historical review is beyond the scope of this section, albeit a brief history of uses of the term in description of observations of brain-behavior interplay offers an insightful perspective on the formation of the term in its current use and a display of adjacent terms and notions associated with it.

Presumably one of the first to use the term plasticity to describe a relationship between the brain with learning and behavior, was the philosopher and psychologist William James in *Principles of Psychology* (1890). He used the term to refer to the formation of new paths in the brain and modification of existing ones, in a process facilitating behavior, while he also speculated that formation of functional associations between neural elements arises when they are simultaneously active. Soon after, Santiago Ramon y Cajal speculated that learning requires formation of new connections between neurons and proposed neuronal activity as a substrate of mental activity (Ramón y Cajal, 1893, 1894b, 1895). About the same time, Italian neuropsychiatrist Eugenio Tanzi in 1893, 4 years before the term synapse was coined and its function as facilitating transmission between neurons was established by C.S Sherrington (Sherrington, 1897), hypothesized that a mechanism, analogous to what we now know as synaptic transmission, facilitates learning through repetitious activity of neuronal paths during practice (Tanzi, 1893). His student, Ernesto Lugaro deepened and enriched his work with an insight of the chemical nature of synaptic transmission and emphasized deeper Tanzi's perspective in relating plasticity to synaptic modifiability (Lugaro, 1898, 1906). Clearly, already in its early uses the term appears in joint contexts with concepts of change, modifiability and functional associations.

Following criticism on such a synaptic theory of learning and prevalence of opposing scientific perspectives in the next decades, research on plasticity, as defined above, resurfaced, with a meaning of neural modifiability underlying learning, in the 1940s. The neurophysiologist

[1] Notions of corporeal malleability in relation to environmental factors and behavior are not a product of modernity, but can be traced back to the humoralist conception of the body and its relation to its environment, including nutrition and climate, as well as its relation to an individual's temperament and mental activity (for a review see Meloni, 2018).

Jerzy Konorksi in 1948 highlighted reactivity and plasticity as properties of the central nervous system and introduced a morphological concept of plasticity, whereby plasticity is associated with the formation and multiplication of synaptic junctions between two neural cells (Konorski, 1948). A year later (1949), the psychologist Donald O. Hebb suggested that strength and effectiveness of a specific synapse might change as a result of neuronal activity, named ever since 'Hebbian synapses' and 'Hebbian plasticity', whereby simultaneously neuronal firing leads to functional association (Hebb, 1949). A few decades later, the neurophysiologist Jacque Paillard, in 1976, postulated how both functional and structural changes deserve the term plasticity only in a context where the system achieves a novel function by transforming its connectivity or changing its elements (Paillard, 1976).

In the course of these decades, invasive animal lesion and deprivation studies examined plasticity manifestations within critical periods, time windows during which the brain is more susceptible to change as it is undergoing maturational modifications in its structure and function (Hensch, 2004; Hubel & Wiesel, 1970; Lorenz, 1935). In a paradigm shifting manner, plasticity became a topic of research beyond critical periods, in adulthood, again in experimental paradigms of lesion and sensory deprivation studies. Exemplary findings of these studies include changes in receptive fields and retinotopic organization following lesions in the visual cortex (Gilbert et al., 1990; Gilbert & Wiesel, 1992; J H Kaas et al., 1990), alterations in tonotopic representations of the auditory cortex (Robertson and Irvine, 1989) and cortical map expansion of the somatosensory cortex (Merzenich et al., 1984). Some of the first studies to explore effects of exposure to enriched or isolated environments and training found changes in dendritic branching, in the number of synapses per neuron and in dendritic length in the adult (Greenough et al., 1979), middle-aged (Black et al., 1990; Green et al., 1983), and aged rats (Greenough et al., 1986). Such studies paved the way to new conceptualizations of changes in brain circuitry occurring throughout the lifespan and motivated studies of human adult plasticity.

Coming to the present and the specific framework of the term that this dissertation adheres to, brain plasticity is constrained to experience-dependent plasticity, denoting any sort of changes in brain structure and function arising as an adaptive response in contexts of increased environmental demands (Lövdén, Bäckman, et al., 2010). This kind of plasticity is to be distinguished from the type of experience-expectant plasticity, tied closely to the brain's developmental timelines, consisting of critical periods for maturation and fine-tuning of sensory and cognitive subsystems. It is also to be distinguished from plasticity describing any sort of adjustive and compensatory modifications taking place in the aftermath of brain injury and loss of functionality. Within this framework, plasticity is triggered by a prolonged discrepancy between the currently available structural and functional repertoire of the brain and the demands posed externally, which cannot be met only by flexible adaptations of the current resources (Lövdén et al., 2010)[2]. In human studies, such environmental demands include skill acquisition and learning experiences, in the sense that these experiences probe either modifications of existing states and representations or emergence of new states and presentations, coding aspects of newly acquired knowledge and skills (Lindenberger & Lövdén, 2019; Lövdén et al., 2020). Within the corpus of relevant literature, the term is in discourse with notions of stability and flexibility. The former denotes any sort of limitations to perpetual changes that would exhaust resources and potentially hinder the stabilization of acquired skills and learning. The latter denotes broadly the capacity to use existing functional repertoire in order to respond to the demands posed.

[2] For the sake of precision, there is a difference between plasticity manifestations as actualizations of the potential that the brain has to undergo such changes, and brain plasticity, denoting the potential as such (Wenger, Brozzoli, et al., 2017).

2 Theoretical, empirical and methodological foundations

2.1 Experience-dependent plasticity in humans

In humans, experience-dependent plasticity has been intensely researched *in vivo*, allowed by advances in magnetic resonance imaging (MRI), with image acquisition parameters exploiting the different magnetic properties of brain tissues, and by the development of sophisticated analysis tools. Although essential in uncovering plastic changes on the macroscale of brain structure and function non-invasively, they offer neither a direct estimation of the fundamental changes in molecular and cellular mechanisms underlying the observed changes on the macroscale nor information regarding the time-course and duration of their occurrence (Tardif et al., 2016; Weiskopf et al., 2021) [3]. Evidence for a multitude of different cellular and molecular mechanisms that presumably underlie the macro-changes observed in humans with MRI, has been accumulated mainly from animal studies (Sampaio-Baptista & Johansen-Berg, 2017; Schaefer et al., 2017).

The structural and functional correlates of experience-dependent plasticity in the brain have been investigated mainly following two approaches in study designs, which capture different aspects of the phenomenon. One approach includes cross-sectional study designs, where a group considered highly trained or expert[4] in a domain is compared to a control group, and long-lasting alterations in brain structure and function presumably resulting from intensive training are examined. The second approach includes longitudinal studies, where an experimental group undergoes some kind of training, the effects of which on brain structure and function are then assessed. Both approaches are restricted by inherent design limitations which call for cautious interpretations and inference. Cross-sectional study designs do not account for predispositions in brain structure and function, offer correlational evidence and are not informative about the trajectories of observed changes (Olszewska et al., 2021). Longitudinal studies, bounded inherently by the high costs of their administration, are often restricted by their data acquisition frequency scheme. This imposes specific assumptions on the time courses of expected plasticity manifestations, which even among investigations of

[3] Recently, further advances in MRI, specifically quantitative MRI, where parameters used in image acquisition have with particular sensitivity on specific tissue properties or molecule concentration, promise to shed more light on the underlying mechanisms (Tardif et al., 2016; Weiskopf et al., 2021), a topic that will be discussed further in the overall discussion (section 7.2).

[4] The construction of the notion of the *expert* is of great interest. Etymologically from the latin word *experiri,* meaning *to try*; *experitus,* as in tried, proven, known by experience, and the ancient Greek *εκ/εξ* + *πείρα* broadly meaning *from within* + *experience* is rooted in the development of mastery in a skill through accumulated experience. For a brief history of psychological and neuroscientific research on defining characteristics of expertise see Skovholt et al., 2016).

plasticity within the same domain, allow for contradictory observations, as for example both increases and decreases in regional estimates of grey matter volume (Criscuolo et al., 2022; Wenger, Brozzoli, et al., 2017).

Although I do not aim for an exhaustive review of studies in the field, in the next few paragraphs I will briefly review studies investigating experience-dependent plasticity in different domains. This will serve as a general framework for the emergence of open questions and for laying the ground for the projects presented in the following chapters.

Changes in grey matter

Structural MRI, mostly by acquisition of T1-weighted images, is commonly used for assessment of grey matter morphology aided by computational anatomy tools like Voxel-Based-Morphometry (VBM) (Ashburner & Friston, 2005; Wright et al., 1995). This way, changes in grey matter volume, density and cortical thickness are estimated. Candidate cellular contributors to observed changes in grey matter morphology include changes in the excitatory-inhibitory balance of local circuits induced for example by neuromodulatory systems and their interactions (Carcea & Froemke, 2013; Froemke & Schreiner, 2015), dendritic spines growth, changes in dendritic length, branching and number of dendritic spines per neuron, morphological modifications of non-neuronal glial cells and capillaries and gliogenesis (Galván, 2010; Schaefer et al., 2017; Robert J. Zatorre, Fields, et al., 2012).

Studies using cross-sectional designs and examining differences in grey matter between professionals or experts in a variety of fields and control individuals, have demonstrated alterations in grey matter structures in brain regions related to the domain under examination. Such alterations are manifested both as increases in metrics used, for example in grey matter volume in London taxi drivers (Maguire et al., 2006), in professional typists (Cannonieri et al., 2007), and in professional handball players (Hänggi et al., 2015), as well as decreases, like in professional chess players and chess masters (Duan et al., 2012; Hänggi et al., 2014; Ouellette et al., 2020) and in professional simultaneous interpreters (Elmer et al., 2014), to name a few.

Longitudinal studies attempting to provide more conclusive proof that observed changes can be allocated to a specific training paradigm, have followed specific groups in naturalistic conditions undergoing intensive learning in their everyday lives. For example, significant increases in grey matter structures were observed for medical students preparing for exams (Draganski et al., 2006) and increases in cortical thickness in conscript interpreters following three months of intense language learning (Mårtensson et al., 2012). In more controlled approaches, a variety of studies have utilized training regimes of various durations and intensities to probe plastic changes in the adult brain. Changes in grey matter metrics of volume, thickness, density and cortical surface in training targeted brain regions have been observed following acquisition of foreign vocabulary (Bellander et al., 2016), spatial orientation (Lövdén et al., 2012; Wenger et al., 2012), video game training (Kühn et al., 2014), learning to juggle (Boyke et al., 2008; Draganski et al., 2004; Scholz et al., 2009), mirror-reading (Ilg et al., 2008), motor training (Hamzei et al., 2012) and complex whole-body balancing training (Taubert et al., 2010).

Changes in white matter

Diffusion weighted imaging (DWI), sensitive to self-diffusion of water molecules in tissues, has advanced the analysis of white matter anatomical features. By fitting tensor models, parameters can be extracted that quantify the directional dependence of water diffusion. Such parameters include fractional anisotropy (FA), reflecting the directional dependence of water, and mean diffusivity (MD), which estimates the average diffusion across all directions. These parameters are modulated by several features of white matter microstructure (Sampaio-Baptista & Johansen-Berg, 2017) and usually higher values of FA and lower values of MD are associated with higher levels of organization of white matter structures and increased myelin or increased packing density of a fiber bundle (Olszewska et al., 2021)[5]. Furthermore, direction of fiber tracts can be estimated, using tractography, tracing the pathways of fiber bundles, based on parameters of principal diffusion direction, corresponding to the underlying fiber direction. In white matter, candidate cellular mechanisms contributing to observed changes in white matter, include changes in axon number, diameter, sprouting, branching and packing density, changes in internode length, in myelination, as well as changes in astrocytes' and oligodendrocytes' morphology or number (Sampaio-Baptista & Johansen-Berg, 2017; Zatorre, Fields, et al., 2012).

In cross-sectional studies, differences in white matter volume, fractional anisotropy, axial and mean diffusivity have been reported amongst others, in ballet dancers in areas underlying premotor cortex (Hänggi et al., 2010), in the cortico-spinal white matter pathway in handball players (Hänggi et al., 2015) and in the superior longitudinal fasciculus in chess players (Hänggi et al., 2014), compared with control populations. In longitudinal studies, increases in fractional anisotropy and decreases in mean diffusivity in training relevant white matter structures have been reported following a 2-months working memory training (H. Takeuchi et al., 2010), visual perceptual learning (Yotsumoto et al., 2008), spatial learning

[5] Although diffusion tensor models have been extensively used, this approach has received criticism in the last years, as parameters extracted are not fiber-specific and thus do not distinguish among individual fibers in voxel-wise metrics. This is particularly important considering manifestations of complex multi-fibers geometry, like crossing-fibers (Raffelt et al., 2017). Newer approaches developed use "fixels" representing specific fiber bundles within a voxel (Raffelt et al., 2017).

(Hofstetter et al., 2013), learning to juggle (Scholz et al., 2009) and cognitive training in domains of episodic and working memory and perceptual speed (Lövdén, Bodammer, et al., 2010), to name a few. Changes in the opposite direction have also been reported, for example, decreases in fractional anisotropy in frontal and parietal regions while training a whole-body balancing task (Taubert et al., 2010).

Changes in function

Apart from experience-dependent plasticity manifestations in grey and white matter structures, effects of expertise, learning and skill acquisition are also evident in functional activation and measures of functional connectivity, namely statistical dependences of the time-courses of neuronal assemblies or brain regions. Functional MRI (fMRI) acquisition protocols rely on the blood oxygen level dependent (BOLD) signal, a metabolic measure of neuronal activity, during task execution and in resting state, meaning in the absence of any external stimulation.

In cross-sectional studies, enhanced activation and connectivity is often reported, as for example in experts in mathematics in frontoparietal and frontostriatal connections (Jeon & Friederici, 2017) and in chess masters compared to novices in various cortical and subcortical brain regions (Duan et al., 2012; Liang et al., 2022). In longitudinal studies following groups undergoing training in their daily lives, increases in activity and connectivity of training relevant areas have been reported for doctors under training to perform endoscopy (Karabanov et al., 2019) and changes in functional responses in a cohort undergoing training to be simultaneous interpreters (Hervais-Adelman et al., 2015).

Increases in functional activation and connectivity among regions or networks of brain regions have been reported based on task-fMRI and resting state fMRI acquisitions, following trainings of different durations in various domain, like shape-identification visual training (Lewis et al., 2009), bimanual skill learning (Irmen et al., 2020), auditory working memory training (Takeuchi et al., 2013) and training balancing tasks (Taubert et al., 2011), to name a few. Further, there are interesting findings regarding the time-courses of occurrence of such changes in activation and connectivity, as increases in early stages of learning have been followed by decreases in subsequent stages while performance remains enhanced. Such findings have been reported in relation to visual texture discrimination training (Yotsumoto et al., 2008), to sequential finger movement motor training (Ma et al., 2010), memory updating training (Kühn et al., 2013) and skillful tool manipulation training (Yoo et al., 2013), among others. Observed are also changes in the connectivity profiles of regions and networks, where while connectivity with some regions or networks increases, it decreases with others, as it has been reported in studies of visuospatial and auditory working memory (Jolles et al., 2013; Takeuchi et al., 2013).

The studies mentioned in this section, span investigations of sensory, motor and cognitive domains and employ a wide variety of experimental designs and conceptual and methodological approaches. This brief overview, apart from acting as an initial orientation in the field of experience-dependent plasticity, has hopefully also featured crucial open questions that emerge when a synthesis of such findings is attempted.

2.2 Auditory plasticity and the particular case of musicians

The particular focus of this dissertation evolves around the modulatory effects of musical training and musical competence on brain structure and function. Already quite early in the field, musicians have been intensively recruited for studying experience-dependent plasticity (Jäncke, 2009). Learning and performing music in a high level of competence assumes a complex set of skills developed sequentially and in parallel over the course of many years, often starting at a young age. Such skills include a fine-tuned auditory perceptual system, control and execution of fine movements, learning and memorizing auditory and motor sequences, sensorimotor synchronization, translating musical notation to action and conveying emotions with sound during performance (Reybrouck et al., 2018), to name a few. Musicians are further considered highly competent in generating expectations based on previous knowledge or from extraction of statistical regularities in musical contexts, detecting violations and efficiently updating their expectations (Vuust et al., 2022). On the brain level this entails that correlates of musical expertise are not to be expected only in the sensory and motor cortices but to extend to higher-order cognitive processing brain regions and regions of cross-modal integration (Jancke, 2016). Furthermore, correlates of musical expertise are to be investigated in the integration of all those subsystems, in the complex array of communications among them, including feedforward and feedback connections (Zatorre et al., 2007).

In an attempt to outline the breadth of regions and networks involved in music-related processing and where neural substrates of expertise can be located, the starting point is necessarily the auditory cortex. The primary auditory cortex lies within the Heschl's gyrus in the posterior part of the superior temporal gyrus (STG) and can be further divided into a central core region surrounded by a belt and a parabelt region (McDermott & Oxenham, 2008). In the primary auditory cortex acoustic features are transformed into percepts, like pitch, and secondary cortices receive projections from the primary auditory cortex. The organization of the auditory system is considered hierarchical in the sense that as the complexity of processing increases, the further anteriorly or posteriorly from the primary auditory cortex it is located (Zatorre et al., 2007). For example, processing of pitch height and chroma take place adjacently from the primary auditory cortex, in planum polare and temporale, while processing of intervallic relationships and melodic contour extends further to both posterior and anterior areas of the supratemporal cortex bilaterally (Liégeois-Chauvel et al., 1998; Patterson et al., 2002; Peretz & Zatorre, 2005). Aspects of music-syntactic processing involve regions important also for language processes[6], like parts of the inferior frontal gyrus bilaterally, the anterior portion of the STG and the ventral premotor cortex (Janata, Birk, et al., 2002; Koelsch, 2011; Liégeois-Chauvel et al., 1998; Peretz & Zatorre, 2005). The auditory system is hypothesized to comprise of two streams, the ventral and dorsal, paralleling the two streams of the visual system (Criscuolo et al., 2022; Kaas & Hackett, 1999; Vuust et al., 2022; Zatorre et al., 2007). The dorsal stream connects the auditory cortex with the parietal lobe projecting to the inferior frontal gyrus, using the supramarginal gyrus as a relay station. It is considered to underlie sensory-motor interactions and to track spectral and spatial aspects of processing. The ventral stream connects the auditory cortex with the middle temporal gyrus and temporal pole which connect to the pars triangularis of the inferior frontal gyrus. The ventral stream is considered specialized in processing auditory object properties and parts of it are shared in language and music processing (Vuust et al., 2022; Zatorre et al., 2007). Music processing involves additionally frontal areas like the dorsolateral prefrontal cortex near and within the inferior frontal sulcus, due to their role in attentional and working memory processes (Criscuolo et al., 2022; Kaas & Hackett, 1999; Salimpoor et al., 2013). Further, structures like the basal ganglia and the cerebellum are involved alongside cortical motor regions, in rhythmic processing, action control, motor timing and movement sequencing (Olszewska et al., 2021; Zatorre et al., 2007). Mesolimbic structures, in coordination with temporal and frontal regions, underlie emotional arousal, reward and pleasure extraction during experiencing and performing music (Olszewska et al., 2021; Salimpoor et al., 2013).

In a recent and insightful metanalysis, Criscuolo and colleagues summarized existing findings regarding the structural and functional correlates of musical expertise along three axes: *the ear*, emphasizing the enhanced frontotemporal auditory system in musicians, *the body*, for the enhanced sensorimotor system in musicians and *the heart*, corresponding to increased recruitment of interoceptive areas in musicians (Criscuolo et al., 2022). In the remainder of this

[6] The relationship between language and music is an active topic of research in many fields, spanning from the shared neural correlates underlying processes in both modalities to their origins and roles in human evolution (Arbib et al., 2013; Leivada, 2021; Patel, 2003).

subsection, a brief review of findings from cross-sectional studies regarding the effects of musical training and expertise in brain structure and function will follow[7].

Grey matter

Frequently reported differences in grey matter metrics among musicians, amateur musicians and nonmusicians lie in the primary and associative auditory cortex bilaterally, often on Heschl's gyrus and planum temporale and regions along the superior temporal gyrus. These differences are observed in metrics of grey matter volume (Bermudez & Zatorre, 2005; Gaser & Schlaug, 2003; Groussard et al., 2014; Palomar-García et al., 2017; Schneider et al., 2002, 2005), thickness (Bermudez et al., 2009), concentration (Elmer et al., 2013), density (James et al., 2014) and surface area (Elmer et al., 2013). Musicians are usually reported to exhibit greater values in these metrics and amateur musicians intermediate ones, in comparison to nonmusicians. Furthermore, these metrics are often positively correlated with expertise status and neurophysiological responses recorded in tasks used (Bermudez & Zatorre, 2005; Elmer et al., 2013; Gaser & Schlaug, 2003; James et al., 2014; Schneider et al., 2005). In addition, they usually correlate with practice intensity and onset of training, as for instance musicians starting training at an earlier age exhibit larger volumes in the right auditory cortex (Gaser & Schlaug, 2003; Palomar-García et al., 2017; Zatorre, 2013)

Differences extend to perirolandic regions, underlying sensorimotor functions including primary motor and somatosensory areas, premotor areas and the supplementary motor areas. In these regions both increases and decreases in grey matter volume (Gaser & Schlaug, 2003; Groussard et al., 2014) and density (Han et al., 2009; James et al., 2014) have been reported for musicians, with decreases in density extending to striatal regions, taken to reflect high automation of motor skills (James et al., 2014). Increased grey matter volume and density in musicians is also found in regions of visuospatial processing and integration of multimodal sensory information like superior parietal regions, the left intraparietal sulcus, the insula, posterior cingulate areas, the lingual gyrus and the fusiform gyrus (Gaser & Schlaug, 2003; Groussard et al., 2014; James et al., 2014; Sato et al., 2015). Musicians are also reported to exhibit greater volume, density and cortical thickness in frontal regions, associated with memory and executive functions, like the middle and superior frontal gyri, associated with monitoring, maintenance and retrieval of musical information, the right mid-orbital gyrus, associated with tonal processing and the inferior frontal gyrus bilaterally, important in syntactic processing, (Bermudez et al., 2009; Groussard et al., 2014; James et al., 2014). Further

[7] The review of only cross-sectional studies in the following subsections is because longitudinal studies of music training recruit individuals without former music training. This offers no parallel to the projects of this dissertation as individuals with previous music training were recruited.

differences in density have been reported in the hippocampus, crucial to memory-related functions (James et al., 2014), and in parts of the cerebellum, associated with representation of fingers and executive functions (Gaser & Schlaug, 2003; Han et al., 2009; James et al., 2014)

White matter

Differences between musicians, amateur musicians and nonmusicians in white matter volume, connectivity and integrity, as indicated by various quantitative parameters, are often found in segments of the corpus callosum, a dense bundle of fibers responsible for inter-hemispheric communication. Musicians in comparison to nonmusicians appear to have increased structural connectivity, as indexed by diffusivity parameters, in segments of the corpus callosum connecting the left and right planum temporale (Elmer et al., 2016; Leipold et al., 2021) and in the genu of the corpus callosum connecting prefrontal cortices (Schmithorst & Wilke, 2002). Further, larger white matter volume in the anterior half of the corpus callosum, connecting premotor, supplementary motor and motor cortices, has also been reported (G Schlaug et al., 1995). Such differences appear influenced by factors of training intensity and age of onset, as intensive musical practice in childhood correlated with greater connectivity and fractional anisotropy in the posterior midbody/isthmus of the corpus callosum (Bengtsson et al., 2005; Steele et al., 2013), while increased fractional anisotropy in the upper splenium of the corpus collosum correlated with intensive musical practice in adolescence (Bengtsson et al., 2005).

Increased fractional anisotropy for early onset musicians has been reported in the corticospinal tract (Imfeld et al., 2009), which originates in frontoparietal cortices and connects the primary motor cortex with secondary motor and somatosensory areas, extending to the spinal cord and is considered the primary motor pathway (Jang, 2014). Differences are also to be found in the microstructure of the internal capsule composed of fiber tracts connecting cerebral hemispheres with subcortical structures like the basal ganglia and the thalamus. Greater fractional anisotropy in the right posterior and anterior limb of the internal capsule have been reported for musicians, which were further correlated with total number of hours of practice during childhood (Bengtsson et al., 2005; Han et al., 2009). Larger tract volume and higher fractional anisotropy values have been reported for musicians also in the arcuate fasciculus, a prominent white-matter tract connecting temporal and inferior parietal cortex with frontal brain regions (Halwani et al., 2011). Furthermore, white matter tract consistency in fibers underlying the ventral auditory stream has been reported to be modulated by expertise level, with higher consistency found in musicians, intermediate in amateur musicians and low in nonmusicians (Oechslin et al., 2018).

Function

Functional correlates of musical expertise are usually manifested in dipole and response magnitudes using electroencephalogram (EEG) and magnetoencephalography (MEG) and in activation strength and measures of functional connectivity using fMRI, both in task execution and in resting state acquisitions.

A series of studies have introduced tasks that tap into core aspects of musical processing, like pitch perception and discrimination, tonal and rhythmic processing. Musicians, in comparison to amateurs and nonmusicians exhibit greater dipole amplitudes and evoked responses during pitch processing (Schneider et al., 2002, 2005) and in detection of structural irregularities, localized in the right middle temporal gyrus, anterior cingulate cortex and right parahippocampal areas (James et al., 2017). Response magnitudes have additionally been found to correlate with volumetric differences in Heschl's gyrus (Schneider et al., 2002, 2005). Superior performance in pitch discrimination is accompanied by increased neural responses to complex tones in the right superior temporal gyrus, Heschl's gyrus, insular cortex, inferior frontal gyrus, and the inferior colliculus for musicians (Bianchi et al., 2017). Enhanced activity in the left middle and superior temporal gyri, the left inferior frontal gyrus, the right ventromedial prefrontal cortex and the insula is found to underlie detection of melodic contour variations and structural irregularities in the closure of musical excerpts (Habermeyer et al., 2009; Oechslin et al., 2013). Strength of activation is also reported to correlate with behavioral measures of musical aptitude (Habermeyer et al., 2009) and to be modulated by expertise level (Oechslin et al., 2013). In tasks of rhythmic processing, musicians appear to rely mainly on activity in perisylvian cortices and basal ganglia (Limb et al., 2006) while audiovisual perception of music and musical gestures in trained musicians involves widely distributed neural representations in auditory, visual and multisensory integration regions (Srinivasan et al., 2020).

In studies examining correlations of musical expertise during unconstrained listening to music, musicians are reported to show increased activation strength in regions of the auditory cortex (Angulo-Perkins et al., 2014), in dorsolateral and inferior frontal regions in the primary and supplementary motor areas (Bangert et al., 2006; Habermeyer et al., 2009), and in parietal areas (Oechslin et al., 2013; Seung et al., 2005). In addition, musicians exhibit greater integration of motor and somatosensory regions (Oechslin et al., 2013). A study using classification analysis indicated that activity in frontotemporal regions, in the caudate nucleus and in cingulate gyrus could differentiate between musicians and controls in relation to processing of musical features, representing low-level (timbre) and high-level (rhythm and tonality) aspects of music perception (Saari et al., 2018). Further, in a task assessing musical familiarity utilizing a wide repertoire of musical pieces, expert musicians had supplementary activations in the hippocampus, the medial frontal gyrus and superior temporal areas bilaterally, suggesting a constant interaction between episodic and semantic memory in musicians (Groussard et al., 2010).

Apart from localized differences in activation, there is also evidence from studies using resting state fMRI to detect differences in functional organization and connectivity among relevant regions and networks. Musicians, in comparison to nonmusicians are shown to exhibit increased interhemispheric connectivity (Leipold et al., 2021), increased connectivity between auditory and motor regions (Palomar-García et al., 2017), as well as among auditory, motor, orbitofrontal and parietal regions. These include the bilateral dorsal anterior cingulate cortex, the insula and the temporoparietal junction, part of the salience network, associated with high-level cognitive control and attentional processes (Fauvel et al., 2014; Luo et al., 2014). Especially in relation to the insula, facilitating integration of multisensory information, increased connectivity is shown to be modulated by years of practice (Zamorano et al., 2017). Musical training has been further associated with increased resting state functional connectivity within networks of multiple cognitive functions, such as vision, language, auditory encoding, working memory, motor control and executive functions (Hou et al., 2015; Hou & Chen, 2021).

Apart from superior performance in music processing tasks, musicians have also been found to outperform nonmusicians or novices in tasks of other domains, including language, memory and executive functions. Specifically, in a metanalysis of 62 longitudinal studies regarding effects of musical training in linguistic processes, musical training was found to benefit speech and prosody processing (Neves et al., 2022). In another meta-analysis of 29 studies comparing musicians to nonmusicians also in memory tasks, the authors reported that musicians were found to perform better in long-term, short-term and working memory tasks (Talamini et al., 2017). Furthermore, the level of musicianship and duration of years of practice have been shown to correlate with performance in tasks assessing executive functions (Criscuolo et al., 2019). Such findings can presumably be attributed to shared commonalities between processing in some domains, like language and music, also sharing neural correlates, or to aspects of musical training where executive functions, memory and attention are crucial, as it is also evidenced in the enhanced recruitment of such brain regions in musicians.

Having outlined the breadth of differences in brain structure and function characterizing musical expertise and being attributed to long and intensive training, it is critical to highlight some contributing factors to the above findings, which are not always possible to be accounted for in cross-sectional studies. Onset of training appears as an important factor for the extent of plastic changes in brain structure and function, as evidenced in studies relating onset of training and years of practice with the magnitude of observed changes in structure and function (Bengtsson et al., 2005; Han et al., 2009; Steele et al., 2013; Zatorre, 2013). Musicians recruited in the abovementioned studies, are both instrumentalists and singers, and within instrumentalists there is substantial variety in the kind of instrument they are engaged with. This plays an important role in which subsystems on the brain level are recruited more and hence differentiates the spectrum of observed plastic changes (Rüber et al., 2015). Another important factor under consideration is individual variability and predispositions in anatomical features and functional circuitry, which especially in the auditory cortex have been found to be predictive of task performance (Zatorre, 2013). Furthermore, successful engagement in music training is influenced by cognitive, personality and socioeconomic factors (Schellenberg, 2020), as well as by genetic differences (Ullén et al., 2016), since not only musical aptitude is found to be correlated with genetic differences but also the amount of music practice has been found to be heritable (Mosing et al., 2014).

2.3 A framework for experience-dependent plasticity

Having laid out findings from multiple studies regarding manifestations of plasticity in brain structure and function in relationship to musical expertise and expertise in other domains, it becomes clear that a synthesis of all the above, even if it would be assumed only within the context of musical expertise, is highly challenging. There appears to be no uniform way in which plastic changes are expressed. Both increases and decreases in metrics of grey and white matter morphology and in measures of functional activation and connectivity are reported for the same regions (Criscuolo et al., 2022), while they are also found for different brain regions within the same cohorts (James et al., 2014; Vaquero et al., 2016). Both increases and decreases observed in various metrics are attributed to the effects of intensive long-lasting training. Interpretations of decreases particularly, portray them as indicative of increased processing efficacy, leading to automated or habitual processing which does not require a lot of neural resources to be allocated. Under closer examination of such findings, it appears that the regions reported to exhibit decreased values in measures of brain structure are mainly part of the motor cortices and striatal regions (Granert, Peller, Gaser, et al., 2011; Hänggi et al., 2010; Haslinger et al., 2004; James et al., 2014; Vaquero et al., 2016), followed by regions in the auditory and visual system and the cerebellum, where less decreases have been observed (Baer et al., 2015; James et al., 2014; Vaquero et al., 2016). An open question that emerges is whether this pattern suggests that unimodal cortices, like the motor one and parts of the auditory system undergo decreases due to increased processing automation, while other parts of the auditory system undergo increases in volume and thickness, reflecting expanded representations and storage of information. In this view, increases in regions of multimodal associative and higher-order cognitive processing could be attributed to enhanced recruitment.

With additional consideration of findings from longitudinal studies, the complexity increases further, as there is wide variability in the timing of occurrence of observed changes as well as the time-courses that they follow. Findings from longitudinal studies are further constrained by the frequency of data acquisition that they follow and they may not always be informative about the permanency of observed changes.

Regarding the timing of occurrence of observed changes, there is evidence that even macroscopic structural changes can occur rather quickly, like for example within minutes in the motor cortex following training for the non-dominant hand (Hamzei et al., 2012), in frontal and parietal cortices after two sessions of balance training (Taubert et al., 2010)or within five days by applying transcranial magnetic stimulation (TMS) in superior temporal cortex (May et al., 2007). Regarding the trajectories of observed changes, evidence from studies implementing neuroimaging acquisition at multiple time points over the course of training, suggests that some changes occurring are rather transient. For example, following visual texture discrimination training, there was an original increase in activation in the primary visual area (V1) during the first weeks which afterwards decreased, while performance remained enhanced (Yotsumoto et al., 2008). In another study using a finger movement training paradigm, the authors found increases in regional activation in the primary and supplementary motor area during the first two weeks, which decreased in the following two, while inter-regional connectivity increased in strength (Ma et al., 2010). In a study following the pattern of structural changes with frequent MRI acquisition while participants practiced left-hand writing and drawing, grey matter in the primary motor cortices expanded during the first 4 weeks and then returned to baseline levels, although task proficiency stayed elevated (Wenger, Brozzoli, et al., 2017).

Similar evidence arises also from a series of animal studies. Analysis of structural MRI data of 3 adult macaque monkeys, learning to use a rake for retrieving food, revealed grey matter increases in task related brain regions followed by decreases, after performance reached asymptote (Quallo et al., 2009). In vivo microscopic imaging of dendritic spines in mice revealed new spines after only a few hours of motor training (Xu et al., 2009). These rapid changes were followed by selective stabilization of new spines while older spines were partly eliminated. This pattern was also observed in the form of learning-related cortical map expansion in rats which occurred rapidly and then renormalized while performance remained stable (Molina-Luna et al., 2008; Reed et al., 2011).

These issues and open questions raised in this subsection are being addressed within a conceptual framework rooted in animal models, developmental theories of plasticity and concepts from reinforcement learning. The proposed exploration-selection-refinement model (Lindenberger & Lövdén, 2019; Lövdén et al., 2020) recognizes stages in experience-dependent plasticity in the neural level which co-occur with behavioral modifications during learning and skill acquisition. At an initial learning stage, neuronal microcircuit, relevant for the skill under training, is widely probed and therefore structurally altered. In this stage, the model predicts increased variability at the neural and behavioral level. This stage is followed by a phase of selection of the best performing relevant circuitry and a possible reduction in communication between primary sensorimotor regions and regions of the frontostriatal system, which support feedback, attention and control mechanisms, necessary during the initial learning phase. During a later stage, functional stabilization of relevant circuitry takes place alongside elimination of surplus circuitry (Lindenberger & Lövdén, 2019; Lövdén et al., 2020; Wenger, Brozzoli, et al., 2017).

Within this framework, findings discussed above like initial increases in macrostructure, can be understood as transient effects, reflecting initial effortful stages of leaning when expansion of macrostructure is necessary, followed by decreases reflecting automation in performance. This can potentially explain findings from cross-sectional studies of reduced grey matter volume and thickness, especially for motor and striatal regions, as well as expansion and renormalization of structure observed in longitudinal studies. In relation to observed cross-sectional differences and longitudinal changes in functional activation, an initial increase in neural activity is taken to reflect local strengthening of activation, followed by a decrease indicating activation only of specific circuitry and reduced needs for further resource allocation. Although regarding functional activation such a prediction does not account for enhanced and widespread activity observed in the neural responses of musicians, as reviewed above, there are a lot of contributing factors to be considered. Such factors include the modality of the brain regions concerned, the functions they serve and the level at which activity represents the amount of resources allocated or activation of further existing representations, which would be expected in groups of highly proficient individuals. These considerations point additionally towards the potential of jointly examining effects of experience-dependent plasticity in brain structure and function. The relationship among differences or changes in brain structure, in functional activation and connectivity may offer an enriched understanding of co-occurring manifestations of plasticity and the different roles they play in supporting superior behavioral performance exhibited by musicians and experts in other domains.

2.4 From brain regions to networks

In this subsection, I intend to expand more on some methodological and conceptual aspects of particular importance for this dissertation. I refer to them as jointly methodological and conceptual because their use entails adopting a specific perspective in examining experience-dependent plasticity. These aspects include a primary focus on resting state fMRI and using functional connectivity methods and metrics from network neuroscience. This approach builds on existing knowledge on the contribution of specific brain regions in aspects of musical processing and changes they undergo due to musical training. At the same time, it extends the scope to include interregional communication and network organization properties as correlates of expertise and as aspects of functional organization undergoing plastic changes.

Resting state fMRI

Resting state fMRI captures the intrinsic low-frequency fluctuations of brain activity exhibiting distinct temporal and spatial organization, often termed resting state networks (Fox et al., 2007; Raichle, 2015). Resting state networks have been related to various aspects of cognitive, social and emotional processes as well as to personality traits (Liégeois et al., 2019) Even more, they are shown to reflect to a high extend the underlying structural architecture of the brain (van den Heuvel & Hulshoff Pol, 2010). Resting state dynamics and organization are considered a sort of baseline internal state, in the absence of external stimulation, which can be shifted when external demands arise (Biswal, Yetkin, et al., 1995; Deco et al., 2011; Greicius et al., 2003). Further, it has been shown that the brain's functional network architecture during task performance is actually predominantly sculptured by the intrinsic network architecture present during rest, with task demands further contributing to observed activation patterns during task execution (Smith et al.,2009, Cole, Bassett, Power, Braver, & Petersen, 2014; Cole, Ito, Bassett, & Schultz, 2016). Furthermore, aspects of functional activity and organization during rest have been related to learning and skill acquisition in a variety of domains, including attention (Rosenberg et al., 2015), memory (Collins & Dickerson, 2019; Meskaldji et al., 2016), visual perception (Baldassarre et al., 2012), social learning of music (Lumaca, Kleber, Brattico, Vuust, & Baggio, 2019), learning of foreign sounds (Ventura-Campos et al., 2013) and motor skill acquisition (Bassett et al., 2011, 2015). In addition, differences in resting state functional connectivity are also evident between groups of different expertise, as reviewed in previous sections. Such findings indicate that resting state fMRI can capture lasting effects of alterations in patterns of activity and connectivity induced by learning and skill acquisition, hence being a valuable tool in understanding aspects of experience-dependent plasticity.

Functional connectivity: static & dynamic

The analytical tool of functional connectivity repeatedly mentioned in studies above, has proven highly valuable for experience-dependent plasticity research. It is shifting the focus from individual brain regions towards studying the interactions among brain regions, which support complex functions and contribute to learning and expertise-like behavior.

Functional connectivity refers to the statistical dependencies between neuronal time series computed usually with measures of correlation, mutual information or coherence (Friston, 1994). Brain regions or neuronal assemblies are presumed to be functionally coupled or part of the same network if their activity is consistently correlated among each other. In this view, behavioral performance can be associated with the strength of interactions among brain regions, which is also shown to be differentiated in groups of different expertise and during learning (Leipold et al., 2021; Palomar-García et al., 2017). Moreover, functional connectivity is constrained by anatomical white matter connections, but is not exclusively defined by it. Co-activation of anatomically non-connected regions has also been observed, especially as long-distance synchronization of activity, although with high within and between subject variability (Honey et al., 2009). Specifically, highly myelinated sensory areas exhibit strong structure-function coupling while less myelinated associative regions exhibit weaker structure-function connections, and constitute examples of functional coupling occurring without being constrained by anatomy (Baum et al., 2020).

Over the years, functional connectivity measures applied either on task or resting state fMRI data have furthered the understanding of interregional interactions and their relation to human behavior and neurodegenerative diseases (Bullmore & Sporns, 2009; van den Heuvel & Hulshoff Pol, 2010). Furthermore, functional connectivity is shown to fluctuate over time (Chang & Glover, 2010), therefore termed dynamic functional connectivity. In this view, neuronal interactions at multiple spatiotemporal scales are crucial determinants of perception, cognition and behavior (Engel et al., 2021). A variety of analytic approaches has been developed capturing different aspects of the temporal dynamics of neural activity (Cohen, 2018). Of particular interest here is the use of measures quantifying connectivity fluctuations and allocating recurring connectivity patterns into configurations or states (Hutchison et al., 2013; Keilholz et al., 2014; Lurie et al., 2019; Preti, Bolton, & Van De Ville, 2017). Distinct 'brain states' have been associated with resting state (Allen et al., 2014; Calhoun et al., 2014), with different aspects of cognition, including working memory (Braun et al., 2015, Shine et al., 2016, Vatansever et al., 2015), cognitive flexibility (Douw et al., 2016), cognitive control (Hutchison and Morton, 2015), selective visuospatial attention (Elton and Gao, 2015), and with motor skill acquisition (Bassett et al., 2011, 2015). Such findings suggest that the use of dynamic functional connectivity may enrich the current scope regarding manifestations of expertise in functional brain organization. For example, skillful musical processing might be associated with distinct brain states, or variability and flexibility in recruitment of brain regions during performance of specific tasks.

Network neuroscience

In the last years, the examination of the functional organization underlying task execution and resting state has been further enriched with analytical tools from network neuroscience. This field draws from complex systems theory, mathematics, computer science, statistical mechanics and systems engineering (Bassett & Sporns, 2017). The brain is viewed as a complex system with multiscale temporal and spatial organization (Bassett & Gazzaniga, 2011) and there exists a multitude of analytic mathematical measures to describe its architecture and the interactions of its components.

With a focus on fMRI specifically, graph theoretical measures offer a framework for modeling the brain as a network, consisting of nodes, brain regions or neural assemblies, and edges, connecting the nodes. Nodes and edges represent the graph elements and their interrelations (Rubinov & Sporns, 2010). In the simplest form, the connections between nodes are either binary, indicating in absolute terms the presence or absence of a connection, or weighted, where the strength of the connection is a function of the coefficient quantifying the connectivity between the nodes. The architecture of a network can then be characterized on the local, mesoscale or global level. Aspects of network organization have implications for its functionality, as they might promote configurations of segregation or integration of the network elements (Bassett & Sporns, 2017; Sporns, 2013).

Overall, the brain is found to exhibit *small-world-network* architecture, promoting a fine balance between integration of its elements and segregation and allowing for adaptation based on current demands (Sporns et al., 2004). It is further found to be *modular*, meaning it can be decomposed into subnetworks or communities. These communities consist of regions that are densely connected to each other and sparsely connected to regions from other communities (Sporns & Betzel, 2016). Modularity is considered as well to promote adaptive response to external demands (Meunier et al., 2010). On the nodal level, there exist a series of metrics characterizing the contribution of individual nodes of the networks they belong to (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010; Sporns et al., 2004). Nodes with few connections within their community are considered *peripheral*. Other nodes, highly connected within their community, are considered *provincial hubs*, facilitating within subnetwork communication, while other nodes, *connector hubs*, play an important role in communication between communities (Larivière et al., 2019; van den Heuvel & Sporns, 2013). For example, nodes within sensory brain areas usually display dense connections within their community, while nodes within associative cortices participate in multiple subnetworks, integrating information and facilitating communication among different communities (van den Heuvel & Sporns, 2013).

Furthermore, graph metrics can characterize network organization dynamically over time. In this case, a graph represents a configuration of a specific time window and is part of a temporally ordered set of graphs spanning multiple time scales, presenting the evolution of element interaction over time (Bassett et al., 2013). In this view, subnetworks are formed and reconfigured continually supporting task execution of various demands or processes that occur during resting state (Mišić et al., 2016; Shine et al., 2016). For example, whole-brain functional network organization was found to change systematically during both a task probing motor execution and a task probing working memory. Increased network segregation was found to underlie successful motor execution and increased network integration to support working memory (Cohen & D’Esposito, 2016).

The application of network neuroscience tools in studies of experience-dependent plasticity can be particularly advantageous. Specifically, regarding musical training and expertise, it offers a quantitative framework to study the interactions within and between the distributed neural circuits which support experiencing and performing music. Promising results of the effects of learning and skill acquisition in brain network organization over time have been reported in relation to motor training. With progressive training and improvements in behavioral performance, higher modularity was observed reflecting more habitual and autonomic processing, and resulting in reduced interactions required among sensorimotor and frontal regions (Bassett et al., 2011, 2015; Telesford et al., 2017). Although such an approach of dynamic network analysis has not been applied in the context of musical training so far, the potential is clear. However, there are studies which have applied graph measures to characterize brain networks statically in relation to musical training and expertise. Musicians compared to nonmusicians are found to differ in a variety of metrics, which suggest more efficient information transmission within and between subnetworks and overall higher integration of auditory processing regions (Alluri et al., 2017; Leipold et al., 2021; Loui et al., 2012)

3 Summary and research objectives

In the previous chapter, I reviewed findings on differences in brain structure and function among groups of musicians, amateur musicians and controls. To summarize, musicians exhibit increases and decreases in measures of grey and white matter morphology and microstructure, as well as in activation strength and connectivity in brain regions associated with various aspects of music processing. The majority of findings attest that manifestations of plasticity are located primarily in core auditory and motor regions, and the pathways that connect them, and extend further throughout the brain to regions supporting multisensory integration, maintenance of information and executive functions. Variability in the findings can be attributed to a multitude of factors, including onset of training, primary instrument, anatomical predispositions, genetics and socioeconomic status, which are fairly difficult to account for in the context of single studies. Further, I briefly discussed some issues and questions that these findings raise and I presented a framework which accounts for some of the observed plastic changes. The importance of such a framework lies beyond its' explanatory power over existing findings. It offers a foundation to raise testable hypotheses on mechanisms of plasticity across domains regarding both brain structure and function. Finally, I introduced in more detail some methodological aspects which are intertwined with the aspirations of this dissertation.

The three studies which comprise the main corpus of this dissertation evolve around functional correlates of musical expertise and training-induced functional plasticity. The motivation behind this focus on brain function is twofold. By looking into aspects of functional activity during task execution, we gain insights into the neural correlates of behavioral performance "in action", while looking into resting state allows for assessment of lasting effects of training on brain's functional organization. By examining longitudinal changes in functional activity and organization, we can better understand how neural circuits are progressively 'tuned' for skillful processing and are adapted to support enhanced performance. In the first and the third study, the focus is on resting state fMRI, given that functional activity and network organization in resting state can be viewed as the brain's "baseline" functional repertoire that may also shape task activations. In the second study, analyses are based on fMRI data acquired during unconstrained listening to music. In all three studies, analyses encompass measures of functional connectivity, static and dynamic, and metrics from network neuroscience. This way, effects of training on brain function and correlates of expertise-like behavioral performance are examined beyond activity in specific brain regions, but in interregional interactions and organization properties of relevant networks. In addition, in the third project longitudinal functional changes are co-examined with changes in grey matter, presenting complementary aspects of plasticity manifestations.

All three studies are based on data acquired in the course of a longitudinal study, the PITCH study, investigating experience-dependent plasticity in the auditory domain, including behavioral assessments, as well as structural and functional MRI measurements. Forty-one participants between 18 and 31 years of age were recruited. Twenty-four of these individuals were attending preparatory courses for entrance exams in Universities of Arts and music conservatories and seventeen individuals were amateur musicians who were actively performing music in everyday life. Over the course of about a year, participants took part in up to five behavioral and MRI assessments. This study presents a unique opportunity to address research questions in an ecological setting, following these individuals during an intensive learning period. In a way, this study allows to open the "black box"[8] of expertise and peek into musical expertise "in the making". The first and the second study are based on behavioral and fMRI data acquired on the first time point when both groups were fully recruited. The third study extends the analysis from this time point to the following two.

The studies of the dissertation are presented in the next chapters ordered by the scope of the process they describe. The objectives of each project unfold as follows:

1. In the first study, I examined whether training induced changes in functional organization are retained in resting state, in the absence of task performance and how they differ between the two groups of different expertise. Specifically, I examined expertise-related differences in functional connectivity and graph-theoretical measures in a network of regions facilitating interval recognition, during resting state. The network was derived based on activations during an interval recognition fMRI task. I hypothesized that the group of aspiring professional musicians would exhibit greater connectivity and global efficiency within this network. Further, I hypothesized that greater connectivity and global efficiency will correlate with behavioral performance in the fMRI task and in a separately acquired behavioral assessment of musical expertise.

[8] The notion of the *black box* used here corresponds to the meaning assigned to it by philosopher, anthropologist and sociologist, Bruno Latour. He used the notion of the *black box* to describe the inaccessibility to knowledge regarding the inner functions of products of scientific and technological work, following their endorsement (Latour, 1987). In a similar way, looking into musical expertise only cross-sectionally, obscures understanding of the gradual changes taking place up to the point of examination.

2. In the second study, I examined how processing demands during unconstrained listening to music are reflected in whole brain connectivity configurations and how musical expertise modulates network organization based on processing demands. This project extends the scope beyond a specific component of music processing, to a more ecologically valid setting of listening to music. Specifically, participants were presented with two musical pieces of different styles and processing demands. I hypothesized that higher processing demands will be reflected in brain states of higher overall connectivity based on evidence from studies investigating effortful cognitive processing. Further I hypothesized that the group of aspiring professional musicians will exhibit correlates of more skillful processing, indicated by graph measures of network integration during listening to the more demanding piece and by utilization of brain regions as network hubs and between subnetworks connectors, tailored by the processing demands, estimated by relevant nodal measures.

3. In the third study, I examined longitudinal aspects of functional plasticity resulting from intensive musical training. I focused on changes over time on the functional connectivity profile of a brain region, which was found to undergo changes in grey matter volume during this time, in the group of aspiring professional musicians. I hypothesized that the functional connectivity of this region with regions relevant for music processing will increase over time, supporting superior behavioral performance for the group of aspiring professional musicians.

A modified version of the following chapter is currently under review in the journal of Brain Structure and Function.

4 Study I: Resting state functional connectivity in an auditory network differs between aspiring professional and amateur musicians and correlates with performance

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4.1 Introduction

Musicians have been a favored group in studies investigating experience-dependent plasticity and the neural correlates of expertise. The years-long intensive training that musicians undergo, often beginning at a very young age, puts great demands not only on specific brain regions in the auditory and motor cortex but also on multisensory and higher-order cognitive-processing brain regions (Jäncke, 2009). Such high demands constitute an ideal condition for triggering brain plasticity, manifested as alterations in brain structure and function in an effort to respond to the challenges posed (Lövdén, Bäckman, et al., 2010).

Musicians, when compared to nonmusicians, exhibit larger volumes in primary auditory cortex residing on Heschl's gyrus, corresponding to differences in neurophysiological responses and musical aptitude (Schneider et al., 2002, 2005). Further differences in volume and cortical thickness in grey matter structures are reported in regions of secondary auditory cortex, motor and visuo-spatial processing as well as in frontal regions (Bermudez & Zatorre, 2005; Gaser & Schlaug, 2003; Palomar-García et al., 2017; Wenger et al., 2021). Differences are also found in white matter architecture and in structural connectivity of the white matter tracts (Abdul-Kareem et al., 2011; Leipold et al., 2021; Schmithorst & Wilke, 2002). In addition, musicians are found to differ in the magnitude of neural responses and functional activation patterns, during a variety of music-related tasks (Bangert et al., 2006; Bianchi et al., 2017; Limb et al., 2006) and during listening to music (Angulo-Perkins et al., 2014).

Interestingly, manifestations of brain plasticity have not only been investigated in the comparison of musicians versus nonmusicians, but also in relation to different levels of musical expertise. In this perspective, musical expertise forms more of a continuum and the contribution of important factors such as duration of training, intensity of training and overall intentions in music engagement, which relate to changes in brain structure and function can be better understood. Differing levels of expertise, that is, professional, amateur, and nonmusicians, appear distinct not only in behavioral measures but also in neural substrates. Differences in grey matter volume between professional and amateur musicians have been reported in motor, auditory and visuospatial regions as a result of practice intensity (Gaser & Schlaug, 2003). In a study recruiting a cohort of professional, amateur and nonmusicians, grey matter volume and neurophysiological responses from the Heschl's gyrus were reported to be modulated by the level of expertise of each group, with amateur musicians exhibiting intermediate values in volume and neurophysiological responses (Schneider et al., 2002,2005). In a series of very interesting studies investigating the neural correlates of different level of expertise using tonal sequences containing different degrees of structural irregularities at their ending, gradual changes in the response amplitudes using fMRI were observed as a function of expertise level (James et al., 2017). Also, a stepwise modulation of brain responses by expertise level in a frontoparietal network was visible, related also to working memory and attention processes, with overall brain activation of amateurs' group being intermediate between the other two, and partly overlapping with the responses of the professional groups (Oechslin et al., 2013). Stepwise increases in grey matter density were also reported in auditory and cognitive regions (James et al., 2014), and white matter tract consistency was also differentiated among the three groups, with increasing consistency corresponding to higher expertise level (Oechslin et al., 2018).

This multitude of plasticity manifestations in cross-sectional and longitudinal studies are complemented by studies examining the factors of predispositions manifested as different conditions in brain function and anatomy (Zatorre, 2013) as well as of genetic differences predisposing individuals to successfully engage in music training (Ullén et al., 2016). Indeed, the amount of music practice has been found to be highly heritable, and associations between musical practice and musical aptitude are highly correlated with genetic differences (Mosing et al., 2014). However, the causal effects of training on changes in brain function and anatomy cannot be refuted, especially under the light of evidence concerning samples of monozygotic twins (de Manzano & Ullén, 2018).

In the last years, resting state functional magnetic resonance imaging (fMRI), capturing the intrinsic low-frequency fluctuations of brain activity exhibiting temporal and spatial organization (Raichle, 2015) has established that the brain's functional network architecture during task performance is actually predominantly sculptured by an intrinsic network architecture that is also present during rest (Cole et al., 2014, 2016). The intrinsic architecture has been related to various aspects of cognitive, social and emotional processes as well as to personality traits (Liégeois et al., 2019). It is regularly included in studies aiming at relating measures of functional organization and graph-theoretical analysis to learning and performance in tasks targeting a variety of domains, including attention (Rosenberg et al., 2015), working memory (Hampson et al., 2006), memory consolidation (Collins & Dickerson, 2019; Meskaldji et al., 2016), perception (Baldassarre et al., 2012), learning (Lumaca et al., 2019; Ventura-Campos et al., 2013) and motor skill acquisition (Bassett et al., 2011, 2015).

Measures of resting state fMRI also have been used in the context of musical learning and expertise, complementing and extending findings from task-fMRI studies by capturing alterations in intrinsic brain organization. Musical expertise is reflected in interhemispheric and intrahemispheric connectivity patterns of functional networks (Leipold et al., 2021). Often, increased resting state functional connectivity in musicians compared to nonmusicians has been reported, primarily concerning the connections between regions of bilateral auditory cortices with the premotor, supramarginal and orbitofrontal regions (Fauvel et al., 2014; Luo et al., 2012; Palomar-García et al., 2017). Apart from regions specifically relating to the perception and execution of music, studies also suggest that musicianship is characterized by altered functional connectivity, both static and dynamic, between brain regions across the entire brain, including also multisensory regions and regions of various cognitive functions, such as memory, language and attention (Hou et al., 2015; Hou & Chen, 2021; Luo et al., 2012), as well as higher order associative regions like the insula, potentially facilitating integration of multisensory information (Zamorano et al., 2017).

With the present study, we set out to investigate whether aspiring professional musicians differ in terms of their resting state functional connectivity of an interval recognition auditory network in comparison to amateur musicians, even though both groups have comparable years of playing an instrument. Interval perception, both as the perception of pitch relations between tones of a chord and as the pitch relation of temporally sequential tones, lies in the core of tonal processing. This includes the perception of the hierarchical arrangement of pitches and chords around the tonal center and their perceived relations, stabilities, attractions and directionalities as well as the scales they evoke (Zatorre, 2003). An extensive amount of research has established that processing of acoustic information begins early in the auditory pathway, with the brainstem as a crucial layover in pitch perception before the primary auditory cortex takes over to transform the acoustic features into percepts (Koelsch, 2011). From there on, processing in the auditory cortex appears to follow a hierarchical organization, beginning in the primary auditory cortex in Heschl's gyrus, crucial for pitch perception and discrimination, and extending both anterolaterally and posteriorly with increasing features' complexity (Chevillet et al., 2011; Peretz & Zatorre, 2005). Next, secondary auditory cortices are consistently reported as crucial in perceptual analysis of tonal information, with both anterior and posterior parts of the superior temporal gyrus, the superior temporal sulcus, the planum polare and temporale being related to processing pitch height differences (Peretz & Zatorre, 2005), in categorical pitch perception (Lee et al., 2011), as well as to processing of consonance and dissonance (Bidelman & Grall, 2014). Regions in posterior Superior Temporal Gyrus and frontal regions are repeatedly reported as supporting tonal processing with working memory and attentional mechanisms, with right inferior lateral frontal areas reported as important for maintenance of tonal information (Janata, Birk, et al., 2002; King et al., 2018; Nolden et al., 2013).

In order to investigate whether resting state functional organization can be an indicator of performance and a neural correlate of musical expertise in interval recognition, we utilized an fMRI task to localize regions in the auditory cortex and beyond, constituting a network specific to listening to and recognizing auditorily presented intervals. We examined the architecture of this network in resting state using graph-theoretical measures and related it to performance in the intervals task as well as performance in another behavioral measure reflecting musical expertise. We expected that the identified network would include parts of the auditory network, prominently the primary auditory cortex and adjacent regions of the secondary auditory cortex, located bilaterally on the superior temporal gyri. We hypothesized that the two groups of the study, aspiring professional musicians and amateur musicians, would differ in terms of network strength and global efficiency. In addition, we hypothesized that stronger functional connectivity in the identified network, reflected in the graph measure of network strength, and more efficient within-network communication, captured by global efficiency, would correlate with better performance in the interval recognition task and with relevant parts of another behavioral assessment of musical expertise.

4.2 Materials and methods

Participants

The 41 participants recruited were between 18 and 31 years of age (M_{age} = 22.35, *SD* = 3.63, 15 female). They were recruited through flyers, mailing lists, project presentations in music schools, and word-of-mouth recommendation in Berlin, Germany. Twenty-four of these individuals were in the process of preparing for the entrance exam for a music conservatory. Seventeen individuals were amateur musicians who were actively performing music in everyday life. All participants either sang or played at least one primary instrument, and had at least five or more years of experience singing or playing the respective instrument. Information on the primary instruments reported by participants in both groups can be found in Table 2 of supplementary material (subsection 4.6). Years of singing or playing a primary instrument were comparable across the two groups, $t(38) < 1$, $p = .68$ (amateur musicians: M_{years} = 12.74, *SD* = 5.97; aspiring professional musicians: M_{years} = 12.04, *SD* = 4.56; one participant in the aspiring professional group did not provide information about his or her primary instrument or years of playing). However, participants in the two groups differed in the daily amount of practice dedicated to instrument playing ($t(39) = 3.7$, $p = .001$, amateur musicians; M_{hours} = 1.2, *SD* = 0.8; aspiring professional musicians M_{hours} = 2.6, *SD* = 1.4) and to music theory learning ($t(39) = 4.91$, $p = .001$, amateur musicians; M_{hours} = 0.2, *SD* = 0.3; aspiring professional musicians

M_{hours} = 1.4, *SD* = 0.6). Therefore, our sample comprises two groups of people who have been musically engaged for approximately the same amount of time. A decisive difference lies in the intensity of the training given the different intentions in their musical practice, with aspiring professional musicians undergoing intensive both practical and theoretical learning with their respective musical instruments in order to be accepted to music university programs. It is therefore not simply the mere amount of time of engagement with music that is characterizing different levels of expertise but rather the intensity of this engagement and the motivation behind it. Participants of both groups did not differ with respect to age, $t(39) < -1.05$, $p = .30$ (amateur musicians; M_{age} = 23.00, *SD* = 3.50, 8 female; aspiring professional musicians M_{age} = 21.92, *SD* = 3.72, 7 female). Regarding handedness, 33 participants were right-handed, 2 were left-handed (one in the group of aspiring professionals and one in the group of amateur musicians) and for 5 participants (3 in the group of aspiring professionals and 2 in the group of amateur musicians) there was no report on their handedness. All participants had normal hearing, did not have any metallic implants, and had not had any psychiatric diagnosis.

Participants were paid up to 200€ for completion of the whole study (including up to 5 measurement time points with 1.5 h of MRI and 1.5 h of behavioral testing). The ethical board of the DGPs (Ethikkommission der Deutschen Gesellschaft für Psychologie) approved the study, and written consent of all participants was obtained prior to investigation.

Behavioral measure Berlin Gehoerbildung Scale (BGS)

Participants' level of music expertise was measured by the Berlin Gehoerbildung Scale (BGS, Lin et al., 2021). The BGS was designed by André Werner, a composer and collaborator of this study. It is informed by music theory and uses a variety of testing methods in the ear-training tradition. The BGS consists of four factor-analytically validated scales, namely, Intervals and Scales, Dictation, Chords and Cadences, and Complex Listening, which together form a second-order factor of general music expertise. For the purpose of this study, we focused on the second-order scale of general music expertise, and first-order scale Intervals and Scales, which can be assumed to assess the same ability as the fMRI interval recognition task, and which comprises of four items: Naming Intervals, Notating Intervals, Naming Scales and Naming and Notating Scales (for more information, see Lin et al., 2021).

fMRI interval recognition task

During the fMRI task, participants had to recognize and name the musical interval characterizing two tones presented. On each trial, after hearing two tones that were either presented successively or simultaneously, participants had to choose among four options presented on the screen and indicate the correct interval label. The stimuli were recorded piano tones from a simulation program and had a standard duration of 1600 milliseconds. After the presentation of the tones, there was a random jitter between 1.5 and 3s, after which the response screen appeared. As soon as participants responded via a button press (or after a maximum of 20s), there was an inter-stimulus interval of 1s and a jitter between 1.5 and 3s, after which the next trial started. Within a total task time ranging up to 20 minutes, 140 intervals were presented.

<u>MRI data acquisition</u>

Magnetic resonance images were collected on a Siemens Tim Trio 3T MR scanner (Erlangen, Germany) with a standard 12-channel head coil. For the structural images, a three-dimensional T1-weighted magnetization prepared gradient-echo sequence (MPRAGE) was used (TR = 2500 ms, TE = 4.77 ms, TI = 1100 ms, flip angle = 7°, bandwidth = 140 Hz/pixel, acquisition matrix = 256 × 256 × 192 mm^3, isometric voxel size = 1 mm^3). After that, an 8-minute resting state acquisition followed while participants had their eyes open and were looking at a fixation cross, using a T2*-weighted EPI sequence sensitive to Blood Oxygenation Level Dependent (BOLD) contrast (TR = 2000 ms, TE = 30 ms, FOV=216 × 216 × 129 mm^3, flip angle = 80°, slice thickness 3.0 mm, distance factor = 20%, voxel size = 3 mm^3, 36 axial slices, using GRAPPA acceleration factor 2). Following an auditory oddball task that is not part of the present study, the intervals task was acquired using the same T2*-weighted EPI sequence as described above. All slices were acquired in an interleaved fashion, aligned to genu splenium of the corpus callosum.

<u>Behavioral data analysis</u>

BGS

We formed unit-weighted *z*-scores for the first-order scale Intervals and Scales by calculating the average of the four *z*-transformed items belonging to this subscale, and the second-order scale of general music expertise by calculating the average of all *z*-transformed subscales. These unit-weighted *z*-scores were subsequently submitted to independent samples *t*-tests to test for group differences between aspiring professionals and amateur musicians.

fMRI interval recognition task

Performance on the fMRI interval recognition task was calculated for each participant as the percent of correct responses, that is the task accuracy, using R (R Core Team, 2020). As the data was not normally distributed and professional musicians showed a ceiling effect, we squared-root transformed the data and used a Mann-Whitney-U test for independent samples to analyze group differences in task accuracy between aspiring professional and amateur musicians. In addition, we calculated the reaction times for each participant using the median across trials and we computed group differences between aspiring professional and amateur musicians in reaction times using a Mann-Whitney-U test for independent samples, as the values were not normally distributed.

fMRI data analysis

Preprocessing

Before starting with the analysis, the acquired structural, task and resting state data were structured according to the Brain Imaging Data Structure (BIDS) specifications (Gorgolewski et al., 2016). Data preprocessing of the task fMRI and rest fMRI data was performed using the fMRIPrep toolbox°20.2.0 (Esteban et al., 2019) with the default processing steps utilizing the software packages FSL, FreeSurfer, ANTs, and AFNI. For further details on each preprocessing step in fMRIprep, please refer to the online documentation under https://fmriprep.org/en/stable/. Briefly, a reference volume and its skull-stripped version were first generated. The BOLD reference was then co-registered to the T_1-weighted anatomical reference image. Head-motion parameters with respect to the BOLD reference volume (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering. The BOLD runs were then slice-time corrected and finally resampled into MNI152NLin2009cAsym standard space with a voxel size of 3mm x 3mm x 3mm.

Several confounding time-series were calculated during preprocessing: framewise displacement (FD), Delta VARiation Signal (DVARS) and global signals were extracted for cerebrospinal fluid, white matter, and whole-brain masks, which were later used as nuisance regressors. In addition, a set of physiological regressors were extracted to allow for component-based noise correction (CompCor, Behzadi, Restom, Liau, & Liu, 2007). No individuals had to be excluded due to motion (no image exceeded 0.3 mm average FD).

The task fMRI data were then spatially smoothed with a 6 mm full-width half-maximum (FWHM) isotropic Gaussian kernel. The resting state fMRI data were further denoised using the eXtensible Connectivity Pipeline (XCP-engine) software. A high-parameter stream (36p) pipeline was used, combining frame-to-frame motion estimates, mean signals from white matter and cerebrospinal fluid and quadratic and derivative expansions of these signals (Power et al., 2014; Satterthwaite et al., 2013), as they were outputted during fMRIPrep preprocessing. The data was also despiked, temporally filtered (0.01-0.08Hz), and spatially smoothed with a 6 mm FWHM isotropic Gaussian kernel.

General Linear Modeling: Group analysis of the interval recognition task

The analysis was performed using SPM12 (Functional Imaging Laboratory, UCL, UK) running under Matlab R2020b (The Mathworks, Inc., Natick, MA, USA). For each subject, a General Linear Model (GLM) was estimated, contrasting the listening conditions (both successive and simultaneous presentation of sound stimuli) versus the response screen. For the analysis, the first four volumes were discarded. In addition, confound regressors modelling FD per volume (Power et al., 2014), realignment parameters (translation and rotation) and the first six anatomical CompCor components were included as regressors of no interest in the individual GLMs. Each of the listening events was coded as an event with zero duration and convolved with a canonical hemodynamic response function. Finally, a high pass filter of 128s was used for the data and first-order autoregression allowed for estimation of temporal autocorrelations. We used a contrast of listening versus response to allow for the localization of a task-relevant network underlying auditory perception and recognition of intervals. We acknowledge that this contrast captures a variety of processes, including pitch perception, interval encoding, maintenance and mental manipulation of the perceived intervals aided by working memory, comparison of the perceived intervals with pre-existing representations/templates of intervallic relationships and labeling/naming the interval. Thus, the brain regions identified by this contrast are not considered exhaustive to intervallic processing. At the group level, we used a one-sample *t*-test to test for significant clusters during interval recognition.

Regions of Interest (ROI) definition

Based on the group level GLM results, we identified the regions involved in interval perception at a threshold of $p < .001$ with a Family Wise Error (FWE) cluster-wise correction of $p < .05$. Additionally, a cluster size limit of 45 voxels was applied. For each of the identified ROIs, following the methodological approach of a variety of studies looking into task-informed resting state fMRI activity (Lumaca et al., 2019; Ramot et al., 2019; Tian et al., 2007; Ventura-Campos et al., 2013; Yuan et al., 2018), a sphere was created using the MarsBaR toolbox for SPM (Oréfice et al., 2016). The center of the sphere was set at the peak MNI coordinate of each cluster and a 5mm radius was used.

Resting state time-series extraction

The Rex toolbox (region-of-interest extraction tool; The Gabrieli Lab, MIT; http://www.alfnie.com/software) was used to extract the time-series of the resting state data from within the above defined ROIs for each participant. The extraction was done in units of percent signal change referenced to the mean value of each ROI (Left Superior Temporal Gyrus, Right Superior Temporal Gyrus, Left Putamen, Left Supramarginal Gyrus, ventromedial

Prefrontal Cortex). For each participant a 5x5 weighted undirected correlation matrix was created using Pearson's correlation coefficient in R (R Core Team, 2020).

Graph Theory Analysis

In order to characterize and compare the auditory network across all subjects, we utilized graph-theory measures. To do so, we used BRain analysis using GraPH (BRAPH) theory (Mijalkov et al., 2017), a toolbox written in Matlab that uses the Brain Connectivity Toolbox codebase (https://sites.google.com/site/bctnet/; Rubinov & Sporns, 2010) to calculate network metrics. In this framework, nodes are the spheres created corresponding to peak activations in the task-relevant brain regions. The edges represent the correlations between the temporal activation of pairs of these brain regions. The correlation matrices of all participants that were used in the calculation of two global measures, were weighted undirected matrix, where the edges indicate the strength of the connections. This way the information of the strength of the connectivity between all nodes is preserved, as the edge weight is a function of the correlation coefficient of the timeseries between two nodes. This way, both stronger and weaker connections are represented in the graph and contribute accordingly to the computation of the graph measures. The absolute values of all correlations were used in the calculation of the metrics.

We computed two global[9] network measures, namely average strength and global efficiency. Network strength was used to characterize how strongly the nodes are connected. The network strength on the nodal level is defined as the sum of the weights of all edges connected to a node. The global network strength was calculated as the average of the strengths of all five nodes for each participant. Global efficiency is used to characterize information transmission between the nodes of the network. Global efficiency at the nodal level defines the efficiency of the information transfer from one region to the whole network, and is computed as the average inverse shortest path length between one node and all other nodes in the network. Global efficiency at the global level, the indicator further used here, is then the average of the global efficiency of all nodes in the graph and is inversely related to the characteristic path length (Latora & Marchiori, 2001).

Statistical significance testing was done by extracting the values of the two graph measures for each subject using BRAPH, square-root transforming them as they were not normally distributed, and then testing for a group difference using a two-sample *t*-test in JASP (JASP Team, 2021, version 0.16).

[9] The network measures are characterized as *global* when they are assessed including all nodes and edges of a defined network, in contrast to nodal measures that assess network characteristics for individual nodes.

Correlations between graph measures and behavior

To establish a connection between graph measures and behavioral performance, individuals' network strength and global efficiency were correlated with their performance in (a) the general music expertise score of the BGS, (b) the Intervals and Scales score of the BGS, (c) the interval recognition fMRI task, and (d) the reaction times of the interval recognition fMRI task, using Pearson's coefficient in the first two cases, and Spearman's rho in the latter two as the fMRI performance data shows ceiling effects and the reaction times are not normally distributed. The reported p values are False-Discovery Rate (FDR) corrected for multiple comparisons using the online tool (https://www.sdmproject.com/utilities/?show=FDR).

Additional Analysis

In order to ensure that any group differences observed in the graph measures would be specific to the interval recognition network and that any relation between the graph measures and behavior would be ascribed to the relevance of this network for behavioral performance, we conducted a control analysis using two other, well established resting state networks, namely the default mode network (DMN) and the executive control network (EN), where we also checked for group differences in graph measures and correlations between those measures with the behavioral ones. Following the publication of De Pisapia and colleagues we chose seven regions representative of the DMN and six regions for the EN (De Pisapia, Bacci, Parrott, & Melcher, 2016; see Table 3 in supplementary materials subsection, for details). The procedure of the analysis is identical with the one described above: spheres of 5mm radius were constructed centered on the peak MNI coordinates of the network regions, the time-series of the resting state data from these ROIs were extracted for each participant, a weighted undirected correlation matrix for each network was created using Pearson's correlation coefficient, the two global measures of average strength and global efficiency were computed and again square-root transformed. Statistical testing for group differences was estimated using a two-sample *t*-test and individuals' network strength and global efficiency were correlated with their performance in (a) the general music expertise score of the BGS, (b) the Intervals and Scales score of the BGS, and (c) the interval recognition fMRI task, using Pearson' s correlation coefficient in the first two cases, and Spearman's rho in the latter as the fMRI performance data shows ceiling effects.

4.3 Results

<u>Behavioral results</u>

Berlin Gehoerbildung Scale (BGS)

Behavioral performance scores on the BGS showed a significant group effect: two-sample t-tests with the unit-weighted z-scores showed significantly higher levels of performance for aspiring professional musicians compared to amateur musicians on the overall score of music expertise, $t(39) = 5.72$, $p < .001$, Cohen's $d = 1.8$ (amateur musicians $M = -0.56$, $SD = 0.46$; aspiring professional musicians $M = 0.4$, $SD = 0.65$), and also on the more specific score of "Intervals and Scales", $t(39) = 6.18$, $p < .001$, Cohen's $d = 1.9$ (amateur musicians $M = -0.74$, $SD = 0.7$; aspiring professional musicians $M = 0.52$, $SD = 0.6$), see Figure 1. Of note, there were two extreme cases that were two but not three SDs away from the mean; these were therefore not considered outliers but were kept in all further analyses. Importantly, though, the group difference also stayed significant when they were excluded from the analysis ($t(37) = 5.686$, $p < .001$, Cohen's $d = 1.64$).

fMRI Interval recognition task

As the behavioral performance data of the fMRI interval recognition task was not normally distributed but showed a ceiling effect, we first square-root transformed them and then used the Mann-Whitney-U test for independent samples to non-parametrically assess group differences in task accuracy (i.e., percentage of correct responses) between aspiring professionals and amateurs. There was a significant group effect on task accuracy in the fMRI interval recognition task (*Mann-Whitney* =40.5, $p < .001$, Cohen's $d = 4.5$). As expected, aspiring professionals (M=83.6, SD= 14.4) exhibited higher accuracy in the task than amateur musicians (M=51.9, SD= 20.5); see Figure 1. There was also a significant group difference in reaction times with aspiring professionals responding faster than amateur musicians (*Mann-Whitney* =292, $p = .02$, Cohen's $d = 4$; aspiring professionals M=3, SD= 1.5, amateur musicians M=4.25, SD= 1.8).

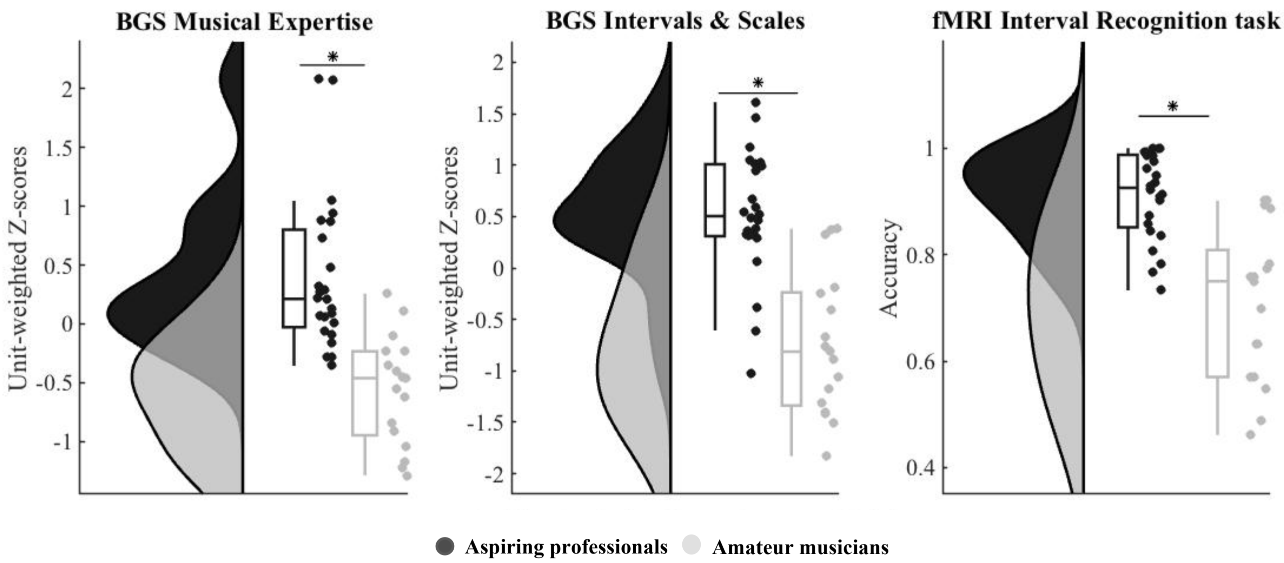

Figure 1. Behavioral performance scores on the Berlin Gehoerbildung Scale (BGS) and the fMRI interval recognition task. In all measures, there was a significant group effect in performance, with aspiring professionals (shown in black) showing higher performance than amateur musicians (in grey), as expected. Group distributions are shown as unmirrored raincloud plots and boxplots with medians and 95% CI with whiskers representing second and 98th percentiles (Allen et al., 2019). Each dot represents a single subject. Asterisks indicate a significant group effect at $p < .001$.

fMRI task results

A whole-brain analysis examining the effects of listening versus response across all participants indicated higher activation during the listening condition in the following clusters: left and right superior temporal gyrus (STG) extending both anteriorly and posteriorly bilaterally including parts of the planum polare, the middle temporal gyrus and the right temporal pole, ventromedial prefrontal cortex (vmPFC), left putamen and left supramarginal gyrus (SMG) (see Table 1 and Figure 2). As can be seen in Figure 2, the cluster in the right hemisphere is rather large and extends also into right putamen. However, due to the thresholds used and the loci of peak activation within the cluster, right putamen did not constitute a separate cluster of activation.

Table 1. Brain regions showing activation during listening in the fMRI interval recognition task, together with cluster sizes and peak MNI coordinates. Significant clusters were identified at a threshold of $p < .001$ with a Family Wise Error (FWE) cluster-wise correction of $p < .05$ and cluster size of $k > 45$ voxels.

Cluster Name	Size	Peak MNI Coordinates
right superior temporal gyrus (STG), *posterior division*	1019 voxels	x=60, y=-40, z=12
left superior temporal gyrus (STG), *posterior division*	292 voxels	x=-67, y=-16, z=4
ventromedial prefrontal cortex (vmPFC)	153 voxels	x=-1, y=48, z=-10
left putamen	112 voxels	x=-22, y=12, z=4
left supramarginal gyrus (SMG)	68 voxels	x=-61, y=-46, z=26

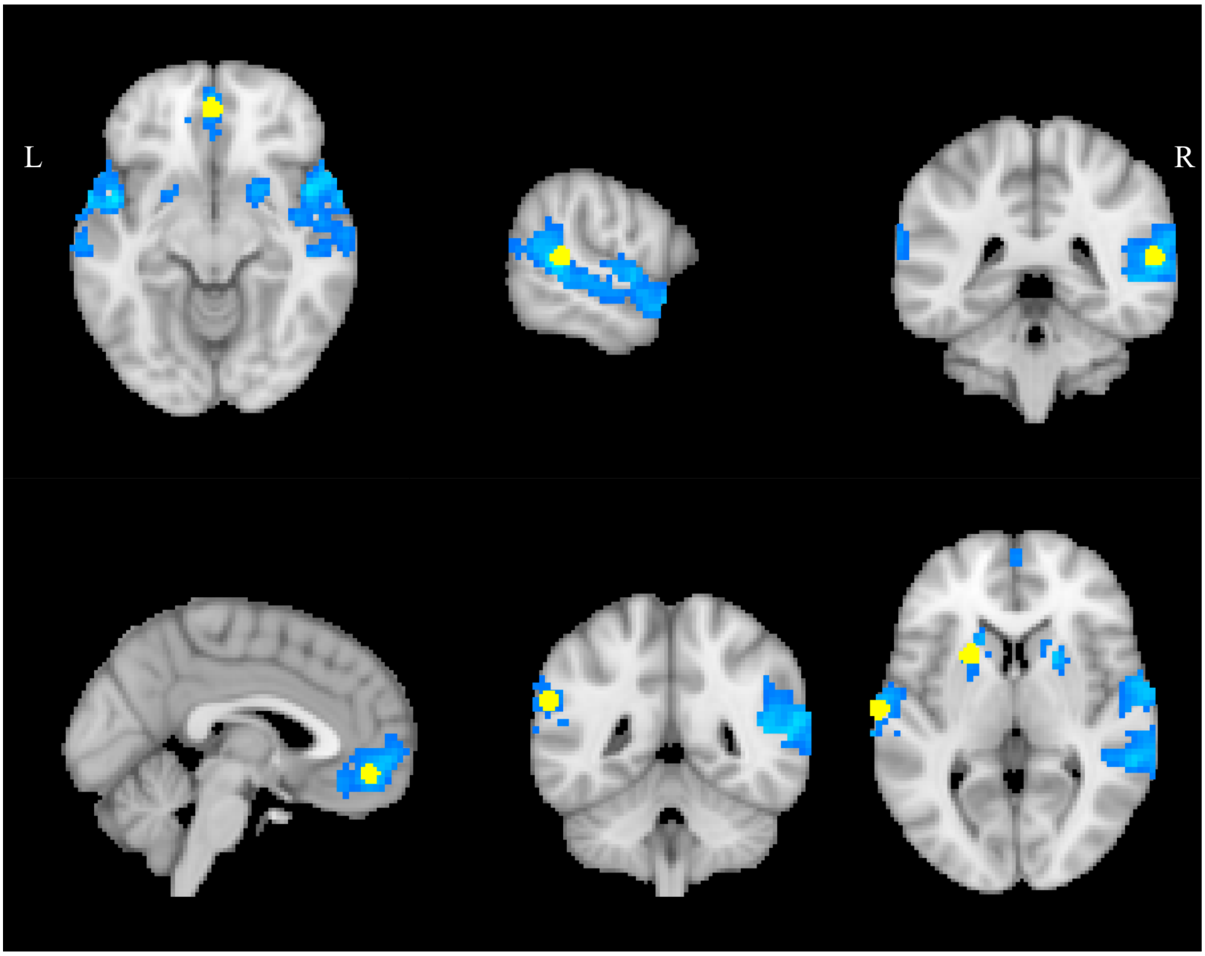

Figure 2. Significant clusters in left and right superior temporal gyrus, ventromedial prefrontal cortex, left putamen and left supramarginal gyrus showing higher activation during listening versus response ($p < .001$, cluster-wise FWE corrected at $p < .05$, cluster size k > 45 voxels). Overlaid on the clusters are the spherical ROIs (in yellow) created around the MNI coordinates of peak activation voxels within the clusters.

fMRI resting state graph-theoretical analysis

Using spheres built around the peak coordinates of the regions showing activation in the interval recognition task GLM, we went on to examine activity and connectivity in those regions in the resting state data. Firstly, the correlations of the extracted time series between each region of the network to the remaining four regions were computed. The average correlation matrix, rendered as a network, provides information about the overall connectivity of the functional network across all 41 participants (Figure 3). In order to characterize the network for each participant in terms of connection strength and efficiency in information transmission and to compare the two groups, graph theory was used and the graph measures of network strength and global efficiency were calculated.

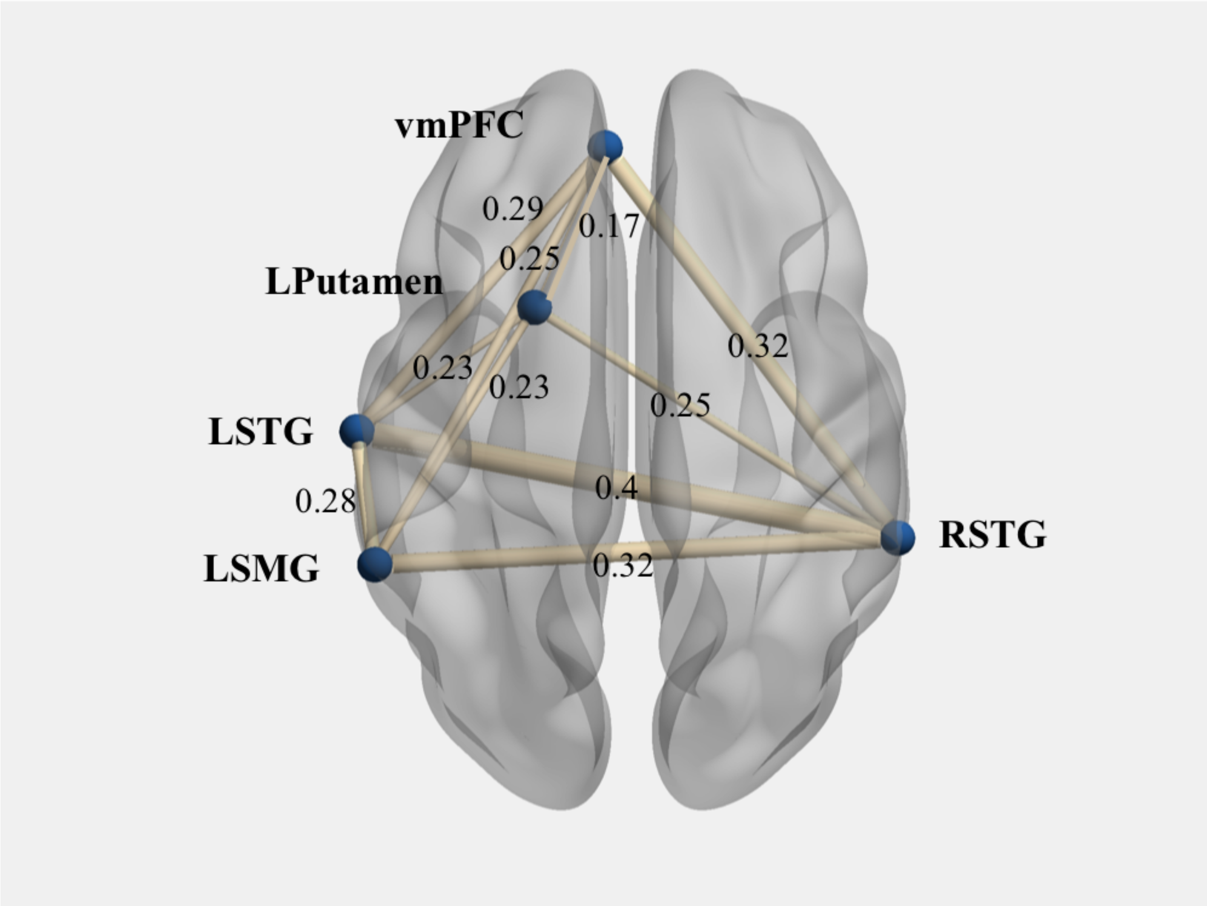

Figure 3. The network of regions facilitating interval recognition as identified based on the fMRI task and its average correlation among all regions for all participants. LSTG: Left superior temporal gyrus, RSTG: Right superior temporal gyrus, LPutamen: Left putamen, LSMG: Left supramarginal gyrus, vmPFC: ventromedial prefrontal cortex). Displayed are also the pairwise correlation coefficients between each pair of nodes (uncorrected). The brain network was visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/)(Xia et al., 2013).

The average network strength and global efficiency was compared between the two groups using two-sample *t*-tests. Aspiring professional musicians indeed showed significantly greater network strength ($t(39) = 2.213$, $p = 0.03$, *Cohen's d* = 0.7; amateur musicians $M = 0.97$, $SD = 0.12$; aspiring professional musicians $M = 1.07$, $SD = 1.13$) and global efficiency ($t(39) = 2.235$, $p = 0.03$, *Cohen's d* = 0.7; amateur musicians $M = 0.51$, $SD = 0.05$; aspiring professional musicians $M = 0.56$, $SD = 0.06$) than amateur musicians (Figure 4).

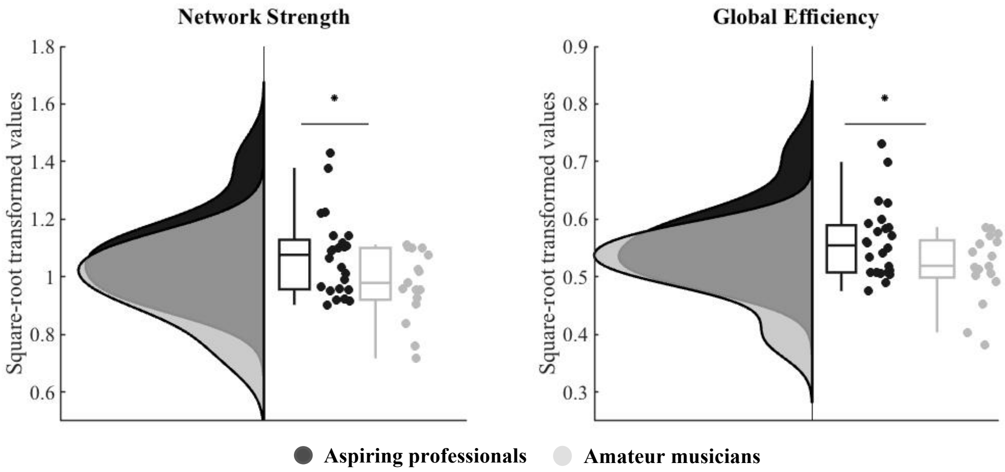

Figure 4. Group differences in network strength and global efficiency. The group of aspiring professionals (in black) showed greater average network strength and global efficiency than amateur musicians (in grey). Group distributions are shown as unmirrored raincloud plots and boxplots with medians and 95% CI with whiskers representing second and 98th percentiles. Each dot represents a single subject. Asterisks indicate a significant group effect at $p < .05$.

<u>Correlations between graph-theory measures and behavioral performance</u>

The Spearman's *rho* correlation coefficient between each individual's network strength on the one hand and accuracy in the fMRI interval recognition task on the other hand revealed a significant positive correlation (*rho* = .36 p_{FDR} = .02). Likewise, we found a positive correlation between network strength and the BGS "Intervals and Scales" scores (r = .35 p_{FDR} = .03), but not with the BGS Musical Expertise scores (r = .26, p_{FDR} =.1), see Figure 5. Additionally, we found a significant positive correlation between global efficiency and accuracy in the fMRI intervals recognition task (*rho* = .33, p_{FDR} = .03), with the BGS "Intervals and Scales" scores (r = .31, p_{FDR} = .04), but not with the BGS Musical Expertise scores (r = .25, p_{FDR} = .1; see Figure 5). There were no significant correlations between graph measures and reaction times in the fMRI interval recognition task.

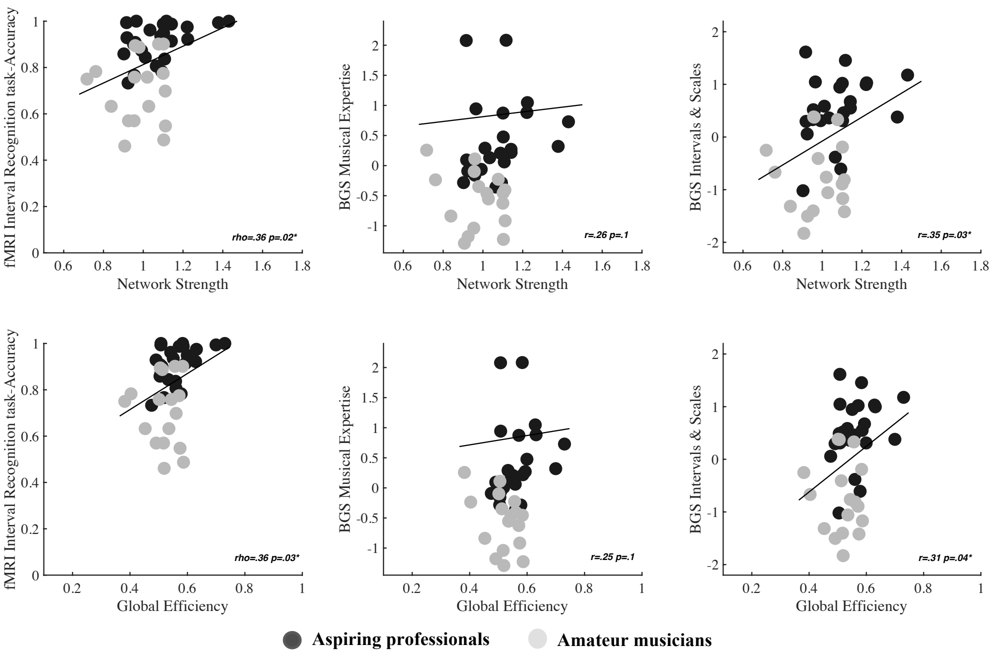

Figure 5. Correlations between graph measures and behavioral performance. Network strength (upper row) and global efficiency (lower row) correlated positively with accuracy in the fMRI interval recognition task (both across groups and within aspiring professionals only) and the BGS "Intervals & Scales" factor, but not with overall BGS "Musical Expertise". Asterisks indicate significant correlations following FDR correction.

<u>Additional Analysis</u>

We also compared average network strength and global efficiency between the two groups in the typical DMN and EN networks using two-sample *t*-tests. Professional musicians and amateur musicians did not differ in terms of network strength in the DMN ($t(39) = 0.413$, $p = .7$, *Cohen's d* = -0.131) or the EN ($t(39) = 0.152$, $p = .8$, *Cohen's d* = -0.048), nor in terms of global efficiency in the DMN ($t(39) = 0.580$, $p = .6$, *Cohen's d* = -0.184) or the EN ($t(39) = 0.6$, $p = .6$, *Cohen's d* = -0.191). There were no significant correlations between DMN network strength and behavioral performance (*rho* = .12, $p = .4$ for fMRI Interval Recognition task, $r = .08$, $p = .6$ for the BGS Musical Expertise and $r = .05$, $p = .7$ for BGS Intervals & Scales). There were also no significant correlations between global efficiency and behavioral performance (*rho* = .12, $p = .4$ for fMRI Interval Recognition task, $r = .07$, $p = .6$ for the BGS Musical Expertise and $r = .09$, $p = .5$ for BGS Intervals & Scales). Similarly, there were no significant correlations between EN network strength and behavioral performance (*rho* = .14, $p = .3$ for fMRI Interval Recognition task, $r = .07$, $p = .7$ for the BGS Musical Expertise and $r = -.03$, $p = .8$ for BGS Intervals & Scales), nor between EN global efficiency and behavioral performance (*rho* = .2, $p = .2$ for fMRI Interval Recognition task, $r = .08$ $p = .5$ for the BGS Musical Expertise and $r = .04$, $p = .8$ for BGS Intervals & Scales).

4.4 Discussion

In this study, we investigated expertise-related differences in resting state functional organization of an auditory network facilitating interval recognition as well as its relation with behavioral performance. First an fMRI interval recognition task was used to localize a network of regions activated during interval recognition, eventually consisting of the left and right superior temporal gyrus (STG), the ventromedial prefrontal cortex (vmPFC), the left putamen and the left supramarginal gyrus (SMG). We then resting state fMRI data and found that network strength and global efficiency differed significantly between the two groups. Moreover, network strength as well as global efficiency were significantly associated with behavioral performance in the fMRI task as well as with the measure of Intervals and Scales of the BGS, but not with the BGS measure of musical expertise. These group differences as well as the correlations between graph measures and behavioral measures were specific to the intervals network, and did not occur within the typical default mode or executive control network.

The two largest clusters of activation reported from the fMRI task lie on the *left and right auditory STG*, extending in both hemispheres in the posterior and anterior parts including also parts of the right *Middle Temporal Gyrus (MTG)*, *Planum Polare* bilaterally and the *right Temporal Pole.* Peak activations in both clusters are located in *posterior STG*. Regions within these clusters correspond to the primary auditory cortices as well as belt and parabelt regions which constitute the secondary associative auditory cortices. Activations in the reported regions are in line with the most prevalent findings in studies regarding various aspects of tonal and general auditory processing, typically with a rightward hemispheric functional asymmetry, as right STG appears more specialized for spectral features processing while the left STG is more specialized for temporal features processing (Zatorre & Belin, 2001). Brain regions like the Heschl's gyrus and adjacent surfaces have been functionally related to auditory pitch perception while pitch changes have been related to activation in the right STG and additionally in right planum temporale and planum polare and anterior parts of the STG (Hyde et al., 2008; Patterson et al., 2002; Warren & Griffiths, 2003). The right posterior STG is reported in addition to play a role in imagery or rehearsal of tones and melodies (Peretz & Zatorre, 2005), auditory working memory (Nolden et al., 2013), and perceptual decision making (King et al., 2018; McDermott & Oxenham, 2008). Overall, interval information processing appears to involve areas anterior and posterior of the supratemporal plane (Koelsch, 2011), where also our clusters of activation extend.

Apart from the superior temporal areas, three additional clusters were found in extra-auditory regions, in the basal ganglia, the medial orbitofrontal cortex and the left supramarginal gyrus. The *left and right putamen*, parts of the dorsal striatum, are related to a wide-range of functions from sensorimotor to decision making and reward processing (Groenewegen, 2003). In relation to audition, evidence from animal studies has established the role of corticostriatal neurons in auditory decisions (Znamenskiy & Zador, 2013) and in integration of multisensory information (Zhong et al., 2014). In humans, putamen activation has been detected in a variety of auditory processes, including beat perception, sensory-motor predictability, finger tapping, music comprehension, tone discrimination, audiomotor coupling, assumed to relate to temporal and sequential aspects of processing (i.e., syntax in language), and musical imagery (Geiser et al., 2012; Kotz et al., 2009; Pando-Naude et al., 2021). The *left SMG*, part of the somatosensory association cortex, apart from its involvement in phonological and articulatory processes (Oberhuber et al., 2016), has been shown to facilitate short-term pitch memory (Schaal, Pollok, & Banissy, 2017; Vines, Schnider, & Schlaug, 2006) and maintenance of pitch information in studies using transcranial magnetic stimulation (TMS; Schaal et al., 2015). The *ventromedial prefrontal cortex (vmPFC),* a region receiving projections from multiple sensory areas and limbic structures, plays a central role in sensory-input integration and in perception-based decision-making (Sharma & Bandyopadhyay, 2020). Animal studies have shown orbitofrontal activation in response to sound and an association of the orbitofrontal cortex, constituting part of the vmPFC, with the primary auditory cortex (Winkowski et al., 2013, 2018). In humans, activation of the vmPFC and ventrolateral PFC has been reported during auditory processes, involving attending to pitch, rhythm and melodies, determining sound length and auditory working memory (Plakke & Romanski, 2014). More importantly, the rostromedial prefrontal cortex has been reported to maintain a topographic representation of the tonality surface (Janata, Birk, et al., 2002). These findings highlight the role of the medial PFC in maintaining tonal contexts and facilitating integration of information necessary for interval perception and identification.

Consequently, all five regions of the reported interval recognition task network have already been associated with various aspects of auditory processing pertinent to the current study in existing literature. We consider pitch and interval processing to be reflected in activation primarily in bilateral STG, short-term maintenance of the auditory information in the left SMG, and integration of information as well as preparation for decision and response in the putamen and vmPFC. Thus, the activation of extra-auditory regions comes as no surprise as these structures mediate different aspects of auditory processing. There exists a rich literature especially regarding the connection between auditory cortex and frontal regions often termed the ventral and dorsal dual stream of auditory processing, in which we suspect our findings to reflect the ventral stream, originating in the primary auditory cortex and projecting to the ventral regions of the frontal cortex (Zulfiqar et al., 2020).

Although a first view on the spherical ROIs created around the voxels with peak activation values gives an impression of general left lateralization of the regions, this does not portray entirely the outcome of the fMRI task analysis. Apart from the left SMG, the clusters of activation were bilateral, as can be seen in Figure 2. The proximity of activation and the size of the smoothing kernel influenced the formation and the extent of the clusters. Under these restraints, the right putamen belonged to the larger cluster extending onto the right STG and the cluster formed bilaterally on the vmPFC was restricted to the left hemisphere, where the peak activation value of the cluster was located. In addition, we did not take into account task-specific demands and task-difficulty for the purposes of this study, which have been pointed out in other studies to impact the lateralization of the observed activity (Angenstein, Scheich, & Brechmann, 2012; Brechmann & Angenstein, 2019). We therefore would like to refrain from making any inferences regarding lateralization of activity.

The group differences in performance in the behavioral task of BGS and in performance in the fMRI task, paralleled by group differences in graph measures of network strength and global efficiency, adds to the rich literature of functional and structural reorganization of the brain in relation to musical training of different intensities and aspirations as well as expertise level (Jäncke, 2009; Olszewska et al., 2021; Schlaug, 2008 ; James et al., 2014; James et al., 2018; Oechslin et al., 2013). Average network strength is computed as the sum of all weights of all edges connected to a node, averaged for all nodes (Maudoux et al., 2012). Thus, the greater network strength observed in the group of aspiring professionals indicates stronger functional connectivity among regions of the interval recognition auditory network, irrespective of task execution. Such a finding has already been established using resting state fMRI, relating musical expertise to increased functional connectivity not only among auditory regions (Luo et al., 2012; Palomar-García et al., 2017; Schlaug, 2008) but also among auditory, multisensory and motor regions (Gottfried Schlaug, 2008; Wenger et al., 2021), prefrontal regions (Klein et al., 2016), insular cortex and parietal regions (Luo et al., 2014). Global efficiency, computed as the average of the inverse shortest path length from a node to all others, averaged for all nodes (Latora & Marchiori, 2001), points towards more direct and efficient communication between the nodes of a network and functional integration. Therefore, the greater global efficiency observed in the group of aspiring professionals suggests a more efficient information flow and communication between the nodes of the network facilitating interval recognition. Hence, aspiring professionals –either as a result of their training or because of their self-selection based on talent– seem to rely on a more connected and efficient network that underlies their better interval discrimination ability, as suggested by the correlations between the graph measures and behavioral performance. This is also supported by the specificity of the observed group differences in graph measures of the interval recognition network but not the DMN or EN, and the correlations between these graph measures and behavior.

So far, only few studies have applied graph measures to characterize brain networks related to musical training and expertise. One study using a paradigm in which participants listened to music clips reported increased degree, clustering, and local efficiency, especially for the left STG in musicians with absolute pitch compared to musicians without absolute pitch (Loui et al., 2012). Another study using a similar paradigm found significantly higher nodal degree for musicians in cerebellar regions, the right temporal pole, the parahippocampal gyrus and the inferior temporal gyrus (Alluri et al., 2017). In a study where graph measures were applied on whole-brain resting state fMRI data, musicians had higher average strength, higher clustering coefficient, and, surprisingly, lower global efficiency in comparison to nonmusicians (Leipold et al., 2021). In yet another study, however, using resting state magnetoencephalography (MEG) data, greater global efficiency was reported for musicians, just as we find here (Paraskevopoulos et al., 2017). In a previous study, using the same resting state fMRI data as the current one and investigating the functional connectivity and graph measures of the left planum polare, which underwent volumetric changes over time, we found that the group of aspiring professionals exhibited significant increases over time in global efficiency and clustering measures (Wenger et al., 2021). This finding speaks in favor of a training-associated, rather than purely talent-based, interpretation of the present results. Still, we do not know whether amateur musicians would have been able to show this change had they been exposed to the exactly identical training environment. Although further research is required to better characterize neural networks underlying auditory processing and musical expertise, we consider the current finding of group differences in graph measures that relate to behavioral outcomes as an important indicator of the potential such approaches have in deepening the understanding of the characteristics of the organization of brain regions underlying specific processes, in relation to different levels of expertise.

The present results also elucidate the relationship between task fMRI and resting state fMRI. Regions co-activated or exhibiting heightened functional connectivity while executing a specific task are thought to form a task-relevant functional network. During resting state fMRI, such co-activation of brain regions also occurs and appears organized in several large-scale resting state networks, reproducible across research institutes and populations (Damoiseaux et al., 2006; van den Heuvel & Hulshoff Pol, 2010). One part of these networks is typically also an auditory one, encompassing primarily bilateral primary and associative auditory cortices and often including other brain regions like insula, prefrontal, sensorimotor, anterior cingulate and left occipital cortices (Maudoux et al., 2012). A series of studies and an impressive meta-analysis of a large number of fMRI studies have shown that task-related activation patterns can indeed be mapped onto resting state networks (Calhoun, Kiehl, & Pearlson, 2008; Cole et al., 2014, 2016; Di, Gohel, Kim, & Biswal, 2013; Simon-Vermot et al., 2018; Smith et al., 2009). Such findings suggest that regions intrinsically connected during resting state become simultaneously activated during task execution. Additionally, individual variability in resting state has been found to be correlated and predictive of individual variability in cognitive and motor tasks (Tavor et al., 2016) as well as in processes of emotional regulation and decision making (Cole et al., 2014). Such findings have led to a conceptualization of intrinsic network architectures, as captured in resting state, that are further shaped and altered during task execution by specific task demands (Cole et al., 2014). We consider the results reported in this study to add further to this literature by demonstrating that an auditory network extracted during execution of the specific process of interval recognition, not only retains its functional organization in resting state, but further that graph measures outlining its strength and efficiency can characterize musical expertise and predict behavioral performance.

Finally, we wish to address some limitations of the current study. As the accuracy data of the fMRI interval recognition task was not normally distributed, the interpretation of the significant correlation between task accuracy with network strength and global efficiency should be taken with a grain of salt. Nevertheless, we see a clear tendency of greater network strength associated with better performance not only in the fMRI interval recognition task, but also the “Intervals and Scales” measure of the BGS. Obviously, the current results do not answer the question whether amateur musicians did not recognize some of the different intervals or were simply unable to correctly name them. Still, the correlation between network strength and global efficiency with behavioral performance suggests a link between the more general feature of music expertise (which includes studying of how to correctly name intervals) and brain networks. Future research should try to disentangle differences between correct perceptual recognition of smaller versus greater intervals, and the ability to correctly name them. Furthermore, we would like to highlight that the network of regions reported here, based on the loci of peak activation within each significant cluster from the task-fMRI analysis, is a network facilitating interval perception and recognition, but is not exhaustive in the regions it includes. The contrast of listening versus response does not allow for a very precise localization of tonal processes or for deciphering between simultaneously and sequentially presented intervals. In addition, although the significant clusters of activity are rather extensive, especially along the STG bilaterally, the spherical ROIs cover only a small part of the clusters, making them indicative of the strength of activation in this region but not very fine-grained in their precision. Finally, we need to acknowledge the basic limitation that participants were not randomly assigned to the different groups, an issue that often arises when comparing groups with different levels of expertise. The decisive difference between the groups is the professional intention which is also reflected in the intensity of daily training, practical and theoretical, which they undertake. This limitation was attenuated, but not overcome, by matching participants in both groups on years of playing music. Given the pervasive presence of gene-environment correlations (Ullén et al., 2016), it is likely that participants in the two groups differed in their propensity to profit from extended musical practice.

4.5 Conclusion

In this study, a functional network defined on the basis of fMRI activation during interval recognition differed in strength and global efficiency between amateur musicians and aspiring professionals. Furthermore, network strength and global efficiency correlated with performance on the fMRI interval recognition task as well as with the ability to name and identify intervals and scales assessed with the BGS, a psychometrically validated test of musical expertise. Together, these findings highlight how task-informed resting state fMRI can capture persisting expertise-associated connectivity differences underlying task execution and relate them to expertise-associated behavioral performance. Aspiring professionals, presumably as a result of their training, seem to rely on a more connected and efficient auditory network that supports expert performance levels. The observed group differences in connectivity and global efficiency at rest in a task-relevant network may point to trait-like domain-specific differences in the intensity and efficiency of neural communication.

4.6 Supplementary material

Primary music instrument		Aspiring professional musicians	Amateur musicians
String instruments	struck (piano)	6	3
	bowed (violin,cello)	5	4
	plucked (gitarre)	3	6
Percussion		3	-
Wind instruments (trompete, saxophone,flute)		4	4
Singing		2	-

Table 2 Primary musical instruments reported by participants in both groups and distributed according to the type of instrument (string instruments, percussion, wind instruments, voice).

Regions	**x**	**y**	**z**	**Network**
Medial Prefrontal Cortex	-1	49	-5	DMN
Posterior Cingulate Cortex	-6	-52	40	DMN
Precuneus	0	-56	28	DMN
Left Precuneus/Posterior Cingulate Cortex	-10	-66	24	DMN
Right Precuneus/Posterior Cingulate Cortex	10	-66	24	DMN
Left Lateral Parietal	-46	-70	36	DMN
Right Lateral Parietal	46	-70	36	DMN
Left anterior dorsolateral Prefrontal Cortex	-27	63	6	EN
Right anterior dorsolateral Prefrontal Cortex	27	63	6	EN

Left dorsolateral prefrontal cortex	-46	38	12	EN
Right dorsolateral prefrontal cortex	46	38	12	EN
Left Inferior Frontal Gyrus	-40	24	-10	EN
Right Inferior Frontal Gyrus	40	24	-10	EN

Table 3. Brain regions of the default mode network (DMN) and the executive control network (EN) with coordinates in MNI space (see De Pisapia et al., 2016) used in an additional control analysis to test the specificity or generalizability of our current findings.

5 Study II: Comparing the neural correlates of listening to music by J.S. Bach and A. Webern: Musical expertise matters

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5.1 Introduction

Listening to music is a particularly complex experience. What begins as a sensory act of extracting and processing acoustic features alongside the auditory pathway, involving cognitive as well as memory processes (Zatorre & Salimpoor, 2013), becomes a complex aesthetic experience. It involves a potentially immersive component, it elicits emotional and physiological reactions and activates the reward-system of the brain (Reybrouck et al., 2021). Although the role of various brain areas in the processing of individual musical features like pitch, tonality, timbre and rhythm perception has been extensively studied (Koelsch, 2011; Peretz & Zatorre, 2005), fewer studies have undertaken the attempt to study more ecologically valid settings in which participants freely listened to music without artificial manipulation of the stimuli, in order to determine the neurophysiological correlates of experiencing music.

Studies investigating patterns of brain activity during unconstrained listening to music have provided some evidence for the potential of this approach to locate brain areas and groups of regions crucial for processing specific features of musical stimuli like musical syntax (Schmithorst, 2005), beat salience (Toiviainen et al., 2020), timbral features, pulse and tonality (Alluri et al., 2012). A few studies have focused on the distinct contribution of frequency bands in processing specific features like repartitioning of rhythm periodicities and key (Zhu et al., 2020), while other studies have used classification techniques to show that different brain activation patterns bear information about different musical pieces (Hoefle et al., 2018), predict timbral and rhythmic features (Alluri et al., 2013; Toiviainen et al., 2014) and identify brain regions relevant for self-referential appraisal and aesthetic judgments (Alluri et al., 2013). The variety of methodological approaches adopted by these studies, each tailored to the different research questions posed, as well as the wide variety of the musical stimuli used, the responses they elicit and the overall cultural extra-musical meaning they carry, do not allow for a convergent view of how listening to music translates into specific patterns of brain activation.

Here, we take a different approach in examining the relation of brain activation and listening to music, without focusing on specific musical features, but rather examining aspects of whole brain organization, utilizing dynamic functional connectivity (fc) and graph measures. Dynamic fc uncovers fluctuations of brain activity over time and thus allows for allocating recurring connectivity patterns into configurations or states (Hutchison et al., 2013; Lurie et al., 2019; Preti et al., 2017). These states have been linked to cognition (Gonzalez-Castillo et al., 2015; Simony et al., 2016), phenotypes (Simony et al., 2016), disease (Hutchison et al., 2013) and brain organization during resting state (Allen et al., 2014; Calhoun et al., 2014). Graph theory, on the other hand, offers a framework for modeling the brain as a network consisting of nodes (brain regions, neural assemblies) and edges (connections) that represent system elements and their interrelations (Rubinov & Sporns, 2010). Within this framework, a variety of metrics are used to characterize local and global features of a network, interactions of its elements and aspects of network organization promoting segregation and integration (Bassett & Sporns, 2017; Sporns, 2013). We use two graph metrics, modularity and average strength, to characterize the states that emerge. Modularity is a measure of network segregation, quantifying how a network can be nearly decomposable into sets of subnetworks/communities comprising of regions that are densely connected to each other and sparsely connected to regions from other modules (Sporns & Betzel, 2016). Average strength is a measure indicative of the overall connectivity of the network (Rubinov & Sporns, 2010).

In addition to characterizing whole brain functional organization during unconstrained listening to music, we set out to investigate how different levels of music expertise influence functional organization while listening to music. There is ample evidence for the modulatory effects of musical training in cortical, sub-cortical and cerebellar structures in measures of grey matter volume and thickness (Bermudez & Zatorre, 2005; Gaser & Schlaug, 2003; Palomar-García et al., 2017; Wenger et al., 2021), in white matter architecture and connectivity (Abdul-Kareem et al., 2011) and in functional activation and connectivity (Bianchi et al., 2017; Olszewska et al., 2021). These findings need to be cautiously interpreted in the presence of potential genetic and anatomical predispositions (Ullén et al., 2016; Zatorre, 2013). In relation to unconstrained listening to music, many studies have focused on activation strength, showing more prevalent activation for musicians in regions of the auditory cortex (Angulo-Perkins et al., 2014), the frontal lobe, the primary and supplementary motor areas (Bangert et al., 2006; Habermeyer et al., 2009) and parietal areas, associated with syntax processing and selective attention (Oechslin et al., 2013; Seung et al., 2005). Furthermore, musicians are reported to show increased strength, local and global efficiency in music-processing brain networks (Gonzalez et al.,2021) and greater integration of motor and somatosensory regions (Oechslin et al., 2013).

In this study, we presented participants with two musical pieces, one by J.S. Bach and one by Anton Webern, and thereby introduced two listening conditions that elicit different processing demands. The piece of J.S. Bach, an example of baroque music composition, belongs to an enculturated and familiar musical corpus for Western listeners, which has been mainly used in music-related neuroscientific research. On the other hand, the piece by A. Webern is part of the movement of compositional innovations of the 20th/21st century, an example of the 2nd Viennese School, and poses a challenging and experimental music experience, composed without following the tonal, rhythmic and form-wise standards of Western music (Mencke et al., 2019). We first conducted a quantitative description of the musical pieces in terms of established components of musical analysis to reveal structural differences between the two pieces and to get a sense of the different processing demands they might require. We then examined how these two listening conditions relate to brain connectivity states by using dynamic fc analysis and corresponding state metrics that quantify transitions between states and time allocated in each. We hypothesized that (i) during listening to the piece by A. Webern all participants will find themselves in states characterized by high integration as a result of the demands posed by this condition, specifically its complexity and unfamiliarity, than while listening to the piece by J.S Bach. Similarly, in terms of graph measures, we hypothesized that (ii) listening to the piece by A. Webern would be related to brain states characterized by higher overall connectivity and reduced modularity in comparison to listening to the piece by J.S Bach. Our hypotheses are rooted in findings relating cognitive demands to whole brain configurations, where greater cognitive effort has been related to the emergence of a more integrated, globally efficient and less clustered configuration (Kitzbichler et al., 2011; Shine et al., 2016).

With respect to the effect of expertise on unconstrained listening to music, we applied static fc analysis and computed two global graph measures, in order to directly compute group differences in network architecture. We expected that (iii) the group of higher expertise will exhibit higher strength and global efficiency, a measure of network integration, during listening to the piece by A. Webern, indicative of more skillful processing. Additionally, we used two nodal graph measures and explored the brain regions playing putative roles for each group in the different conditions. We used the centrality graph measure of nodal degree, which provides indication on which brain regions act as network hubs, occupying central positions in functional organization and information transmission (Power et al., 2013; van den Heuvel & Sporns, 2013), and the measure of participation coefficient, indicating which regions facilitate communication between subnetworks, acting as between-modules connector hubs (van den Heuvel & Sporns, 2013). We expected that in these nodal graph measures, (iv) the group of higher expertise will exhibit higher nodal degree and participation coefficient, on a variety of brain regions, crucial for music processing, throughout the brain, especially in the condition of listening to A. Webern, suggesting utilization of the available functional repertoire, presumably enhanced by training, to meet the demands posed by the listening condition.

5.2 Materials and methods

Participants

In the current set of analyses, we investigated the differences in listening to a baroque musical piece by J.S. Bach and a piece by A. Webern of the 2nd Viennese School of music, in two different groups of participants: aspiring professional musicians preparing for entrance exams in order to study at any University of Arts and amateur musicians. Information about the participants recruited can be found in subsection 4.2 (chapter 4), as all three projects of this dissertation are based on data acquired within the same study.

During the fMRI data acquisition participants experienced two listening conditions. During the first one, they listened to a piece by Johann Sebastian Bach, the Harpsichord Concerto in E-major, BWV. 1053 Allegro, bars 1-321, a piece of the baroque music genre, for a duration of 5 minutes. In the second condition, they listened to a piece by Anton Webern, namely Variations Op. 30, bars 1-134, a piece belonging to the Second Viennese School, likewise for a duration of 5 minutes. We would like to emphasize that the more general labelling of those two specific pieces as "baroque" versus "Second Viennese School" is simply done to ease the understanding and is not meant as an indication for broader generalizability.

fMRI Data Acquisition

All MR images were acquired on a 3T MRI scanner system (Siemens Tim Trio, Erlangen, Germany) with a standard 12-channel head coil. The MR measurement protocol included a T_1-weighted structural scan and a resting-state acquisition. As structural images, a 3-dimensional (3D) T_1-weighted magnetization prepared gradient-echo sequence (MPRAGE) of 9.20 min was used with the following parameters: repetition time (TR) = 2500 ms, echo time (TE) = 4.77 ms, inversion time (TI) = 1100 ms, flip angle = 7°, bandwidth = 140 Hz/pixel, acquisition matrix = 256×256×192, isometric voxel size = 1 mm^3. We used the pre-scan normalize option and a 3D distortion correction for nonlinear gradients. Whole brain functional images were collected using two T_2*- weighted EPI sequences of 5 min each, sensitive to BOLD contrast with the following parameters: TR = 2000 ms, TE = 30 ms, FOV=216×216×129 mm^3, flip angle = 80°, slice thickness 3.0 mm, distance factor = 20%, voxel size = 3 mm^3, 36 axial slices, using GRAPPA acceleration factor 2. Slices were acquired in an interleaved fashion, aligned to genu splenium of the corpus callosum.

fMRI preprocessing

The MATLAB toolbox Data Processing Assistant for Resting-state functional MRI (DPABI) was used (Yan & Zang, 2010) which is based on SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (REST; Song et al., 2011). The resting state data were preprocessed using DPABI V4.3 (Yan, Wang, Zuo, & Zang, 2016) with MATLAB 2018a (The MathWorks, Sherborn, MA, USA). The first 10 time points of MR recording (20 seconds) were discarded to allow magnetization to approach a dynamic equilibrium and to allow participants to adapt to scanning noise. The remaining volumes were corrected for different signal acquisition times and then realigned. Individual structural images were co-registered to the mean functional image after realignment. The transformed structural images were then segmented into grey matter, white matter, and cerebrospinal fluid (GM, WM, and CSF; Ashburner & Friston, 2005). To regress out the nuisance signals, head motion, respiratory and cardiac effects, we used the Friston 24-parameter model (Friston et al., 1996) and signals from WM and CSF. In addition, linear and quadratic trends were regressed out to account for low-frequency drifts of the BOLD signal. The images were spatially normalized to the Montreal Neurological Institute (MNI) space and resampled to 3x3x3 mm^3. Finally, spatial smoothing (FWHM kernel: 4 mm) was applied to the functional images and temporal filtering (0.01–0.1 Hz) was performed on the time series.

Musical feature analysis of the two pieces

Analysis of the two music pieces was conducted with the MIR toolbox (version 1.8.1) (Lartillot et al., 2008; Lartillot & Toiviainen, 2007) running under MATLAB 2019b (The Mathworks, Inc., Natick, MA, USA). This toolbox includes an integrated set of functions written in MATLAB, dedicated to the extraction of musical features from audio files. The features relate to established elements in music analysis such as dynamics, timbre, pitch, tonality, rhythm and form. We extracted a subset of features from the categories of tonality, rhythm and form for a descriptive overview of the two musical pieces, highlighting the differences in their tonal and rhythmic composition and their self-similarity, which translate to different listening experiences[10]. From the tonality features we extracted the chromagram and key clarity. The chromagram, or also harmonic piece class profile, shows the distribution of energy along pitch classes and is computed in a logarithmic scale using fast Fourier transformation (FFT). Key clarity gives an estimation of the presence of each key in the signal at any given moment. Key clarity is calculated based on the pitch chromagram and the Krumhansl-Kessler algorithm matching pitch class profiles to key profiles (Krumhansl, 2001; Toiviainen & Krumhansl, 2003), using a window size of 5s and a hop factor of 33%, following Lartillot and Toiviainen (2007). From the rhythmic features we extracted the pulse clarity,

[10] Of course, the features extracted are by no means descriptive of what constitutes a whole experience of listening to music. They are mere indicators of some points of difference between the two musical pieces, facilitating generation of hypotheses regarding differences in the neural correlates of listening to the two musical pieces. The differences highlighted by this analysis do not contain or suggest any evaluation or judgment regarding how individuals experience music belonging to these musical genres, or the pieces per se.

which gives an estimation of rhythmic clarity, indicating the strength of beats. It is computed using the maximum correlation value in the autocorrelation curve as heuristic (Lartillot et al., 2008), using again a window size of 5s and a hop factor of 33. Finally, we extracted the higher-level feature of self-similarity, computed based on the frequency spectrum of the music pieces, depicting the similarity between all possible pairs of frames of each music piece.

Assessing neural differences between listening conditions

Dynamic Functional Connectivity Analysis

After preprocessing the data, we extracted the time courses of 112 brain regions taken from the Harvard Oxford atlas (Desikan et al., 2006) for each participant and during both listening conditions, using DPABI V4.3. These were further analyzed with the DynamicBC toolbox (Liao et al., 2014) under MATLAB 2019b, computing the dynamic functional connectivity using a sliding window approach, with a window length of 60s moving in steps of 1 TR (2s), *across both musical pieces*. Further, the dynamic functional connectivity matrices of all subjects underwent k-means clustering analysis, which collapses the temporal dimension of dynamic connectivity matrices into several connectivity maps describing the recurring patterns of activation during listening to the musical pieces (Allen et al., 2014; Liu & Duyn, 2013) – referred to from here on as states. The optimal number of cluster partition was 2 and was based on the convergence of four distance measures: Squared Euclidean distance (k=2), Silhouette index (k=2), Calinski-Harabasz index (k=2), and Davies-Bouldin index (k=2).

Graph measures and state metrics on dynamic FC analysis

We sought to characterize each state in terms of segregation and overall connectivity by computing the graph-theoretic measures modularity index and average strength, using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/, Rubinov & Sporns, 2010). Modularity index is a measure of the degree to which a network can be subdivided into communities, namely non-overlapping subnetworks, in a way that maximizes the number of within-subnetwork edges and minimizes the number of between-subnetwork edges. Its computation follows the calculation of community structure using a fast multi-iterative generalization of the Louvain community detection algorithm (Blondel et al., 2008; Newman, 2006; Reichardt & Bornholdt, 2006). The strength is a measure of the magnitude of the connectivity between two nodes and the average strength reflects the magnitude of the connectivity of the whole network by averaging over all possible pairs of nodes. On the nodal level, strength is computed as the sum of weights of all edges connected to a node; on the whole network level, the strengths of all nodes are averaged (Rubinov & Sporns, 2010). After setting negative correlations to 0 as is common practice in order to compute the modularity index, modularity index and average strength were calculated for each subjects' connectivity matrices of all windows, within each state, and these were then averaged for each subject state-wise. Subsequently, two-way analyses of variance (ANOVAs) were conducted to estimate the effects of listening condition and state as well as their interaction in terms of modularity and average strength, followed by post-hoc Tukey-Kramer tests, because of unequal sample sizes, since each participant was included in the statistical tests only for the states they actually found themselves in.

Further,three commonly used metrics were calculated to characterize participation of individuals in the states based on the two listening conditions: (i) transition number (i.e. a participant's number of transitions between each pair of states), (ii) dwell time (i.e. average number of consecutive time windows a participant spent in a particular state before switching to another state), (iii) frequency (i.e. average number of time windows a participant spent in a state, expressed as fraction). Differences in state metrics between listening conditions, that is between listening to the piece by J.S. Bach or A. Webern, were computed using paired-sample *t*-tests.

<u>Assessing expertise-related neural differences in listening to music</u>

Graph theory analysis of static fc

We used a static fc analysis for each listening condition separately and examined expertise differences in global (that is, whole-brain) and nodal graph measures. In doing so, we aimed to zoom in on specific regions that acted as hubs, occupying a central position in network organization, and as connector hubs, assisting between modules communication, and demonstrate expertise differences therein.

Network construction for each listening condition separately

The network construction and graph analyses were carried out using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/, Rubinov & Sporns, 2010). Time courses were extracted for each of the 112 regions of the Harvard Oxford atlas (Desikan et al., 2006) and Pearson's *r* correlation coefficient was computed on the time-courses for each pair of regions (ROIs), resulting in a 112x112 correlation matrix. Following Bassett and Gazzaniga (2011), *t*-tests were calculated on the correlation coefficients for each pair of ROIs in the connectivity matrix of each participant and FDR-correction was applied to the *p*-values, such that only those correlations were retained that remained significant, resulting in weighted undirected connectivity matrices. Negative weights were again converted to zeros, a prerequisite to compute graph measures like modularity.

Network analysis

To characterize expertise-related differences on the whole brain graph, we chose *2 global graph metrics*: average strength and global efficiency. As described above, average strength was computed as the sum of the weights of all edges connected to each node and then the average of strengths of all nodes was computed (Rubinov & Sporns, 2010). Global efficiency is a measure of information transmission between the nodes of the network. At the nodal level, it characterizes the efficiency of information transfer from one region to the whole network and is computed as the inverse of the average shortest path length between one node and all other nodes in the network. Global efficiency at the global level is the average of the global efficiency of all nodes in the graph and is inversely related to the characteristic path length (Latora & Marchiori, 2001). Expertise differences for both conditions were assessed using two-sample t-tests. Additionally, for the J.S. Bach listening condition expertise differences were assessed using a Mann-Whitney-U test for independent samples, as the values were not normally distributed.

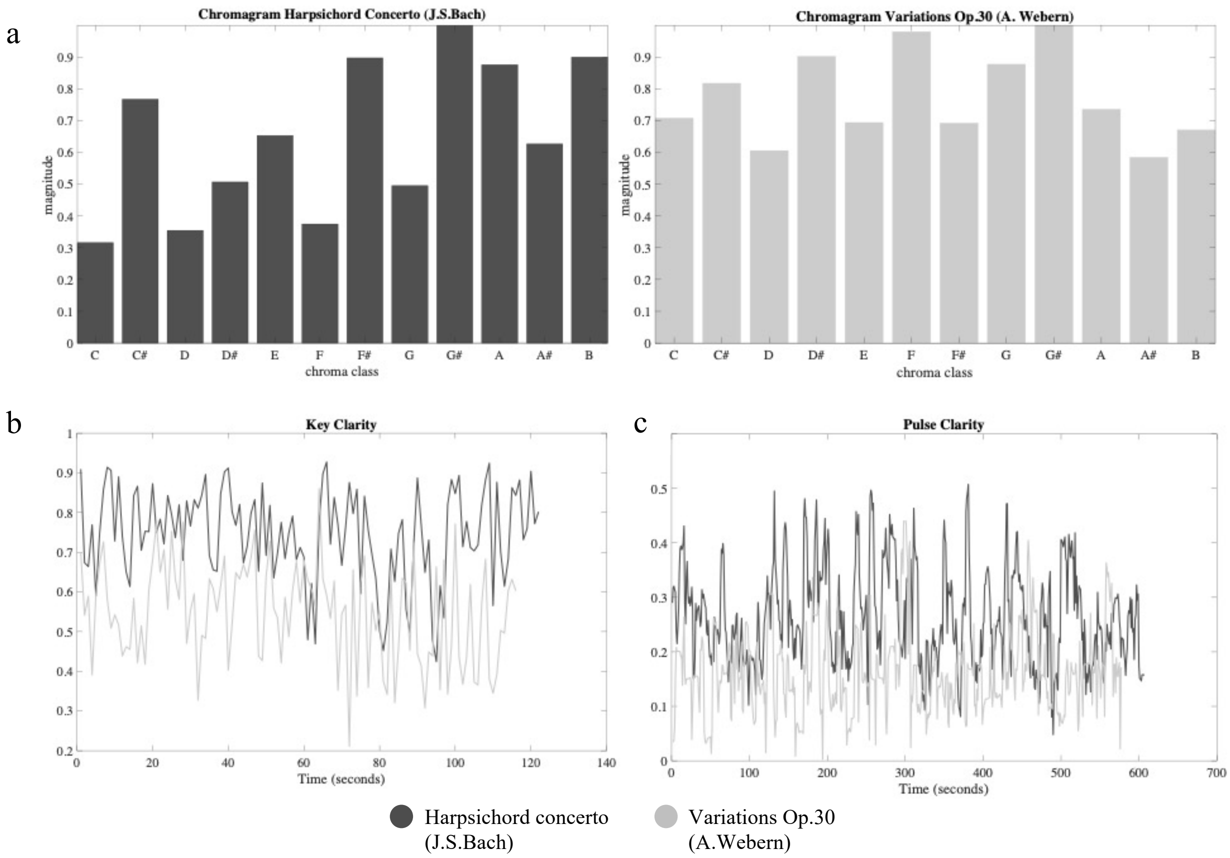
In addition, we computed two nodal metrics for each participant in each condition to assess hubs and connector hubs, namely degree and participation coefficient. The degree or degree centrality refers to the number of edges connected to a specific node. The weights of the connections were ignored by binarizing the connectivity matrix so that only edges with nonzero weights were considered connected. Degree is considered a proxy of the centrality of a node, indicating either that it is a hub within its community (provincial hub), connecting primarily with nodes within its module, or that it plays an important role in whole brain network organization (van den Heuvel & Sporns, 2013). Participation coefficient is a measure of the degree to which a node displays a diverse connectivity profile, communicating with nodes of different modules/communities. Nodes with high participation coefficients are thought of as connector nodes, potentially transmitting information between modules (van den Heuvel & Sporns, 2013). Participation coefficient measures the uniformity of the distribution of connections of a node to nodes from all partitions (Guimera & Nunes Amaral, 2005) and is computed following calculation of community structure (Blondel et al., 2008; Reichardt & Bornholdt, 2006).

For each subject, we computed one sample *t*-tests on the measures of nodal degree and participation coefficient for each node and subsequently corrected for multiple testing using FDR-correction. We tested for expertise differences for each listening condition separately using two-sample *t*-tests on the degree and participation coefficient for the nodes surviving statistical testing and FDR-correction. Additionally, we also tested for differences between the two listening conditions regarding degree for each expertise group, using paired-sample *t*-tests, to assess how groups of different expertise shift their hub profiles based on condition demands.

5.3 Results

<u>Musical feature analysis of the two pieces</u>

Analysis of the two musical pieces entailed the extraction of tonality and rhythmic features, providing a quantitative description of various aspects of the listeners' experience. As can be seen in Figure 6a, the chromagram clearly showed differences between the two pieces: there was more variation in the distribution of energy along pitch classes in the piece by J.S. Bach, while in the piece by A. Webern the pitch classes were more equally represented, as expected in the composition style which does not follow tonal hierarchies. Key clarity, as an estimation of the presence of each key in the signal, differed between the two pieces with the piece by J.S. Bach exhibiting higher mean value (M=0.745 SD=0.115) than the piece by A. Webern (M=0.546 SD=0.12; Figure 6b). As for rhythmic features, we found that the piece by J.S. Bach exhibited a higher mean value of pulse clarity (M=0.264 SD=0.08) than the piece by A. Webern (M=0.161 SD=0.07; Figure 6c). Finally, the frequency spectrum similarity matrix for the piece by J.S. Bach clearly showed higher self-similarity in comparison to the piece by A. Webern (Figure 6d).



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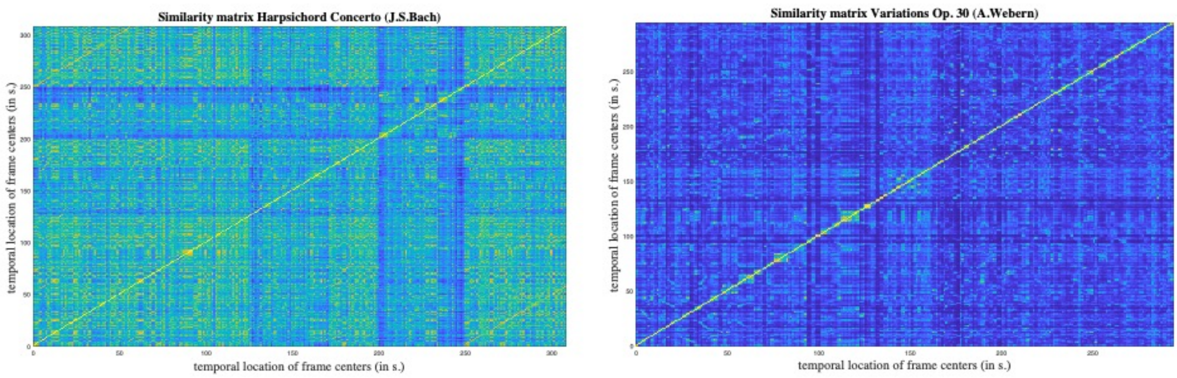


Figure 6. Musical pieces analysis by means of automated extraction. 1a: Chromagram depicting the distribution of energy along pitch classes for the piece by J.S. Bach (on the left) and by A. Webern (on the right). 1b: Key clarity estimated for both pieces, with overall higher values for the piece by J.S. Bach (dark grey color). 1c: Pulse clarity estimated for both pieces, with overall higher values for the piece by J.S. Bach (dark grey color). 1d: Similarity matrices for both pieces based on the frequency spectrum, with higher self-similarity for the piece by J.S. Bach (on the left).

Neural differences between listening conditions

Dynamic functional connectivity analysis

The results of the dynamic functional connectivity analysis and the subsequent k-means clustering identified two most prominent network configurations during both listening conditions. One occurring at a mean frequency of 37,99% and the other at a mean frequency of 62,01% (Figure 2).

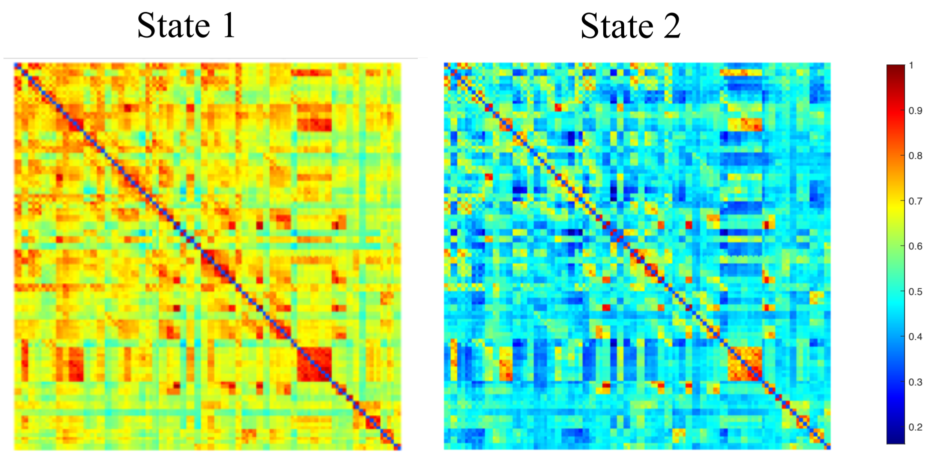
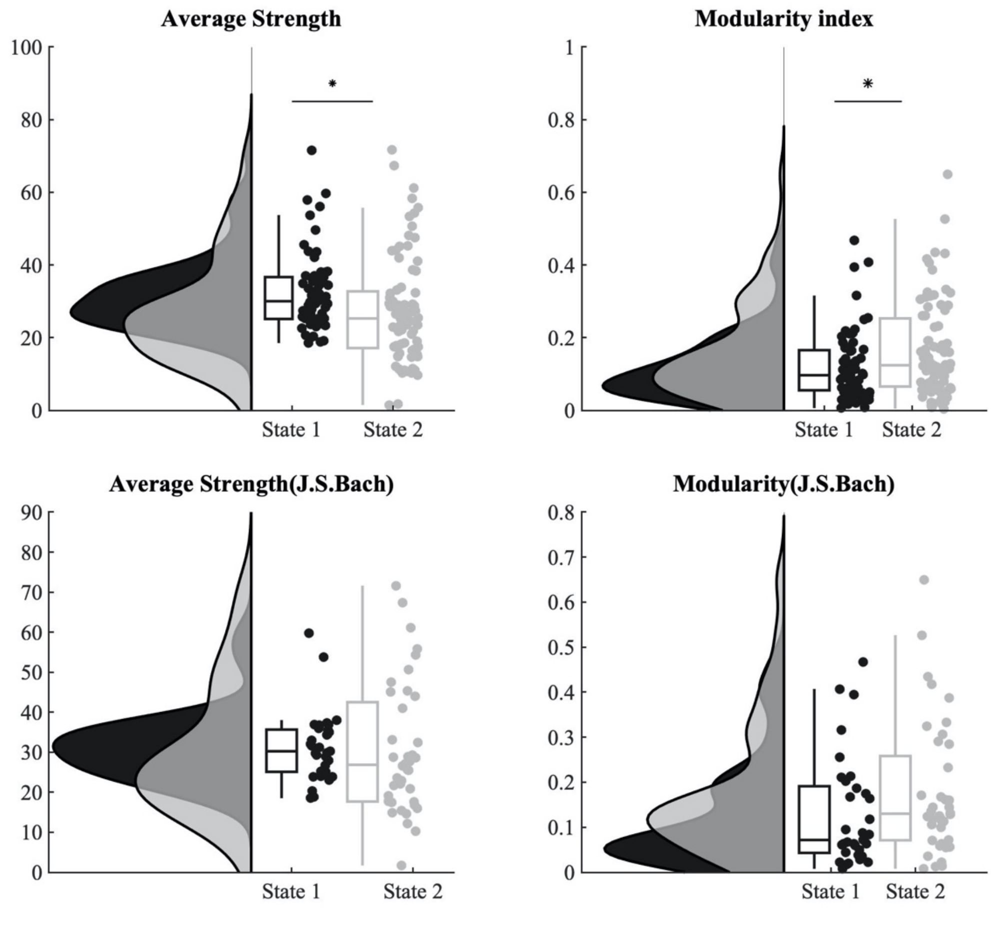


Figure 7. Brain states detected with dynamic functional connectivity analysis using sliding window approach and subsequent k-means clustering of the connectivity matrices of each time window, collapsed for both listening conditions. The matrices represent the 112 ROIs from the Harvard Oxford atlas, are uncorrected and displayed for visualization purposes. The first state occurred at a total frequency of 37.99% and the second state at a total frequency of 62.01% of the time.

Graph measures and state metrics comparing listening conditions

In order to characterize each state in terms of segregation and overall connectivity, we computed the modularity index and average strength for each subjects' connectivity matrices of all windows and averaged for each subject state-wise. The two states differed significantly in terms of modularity index ($F(1,1) = 5.98$, $p = .015$) and average strength ($F(1,1) = 5.14$ $p = .024$; see Figure 8). There was no significant difference between listening conditions or any interaction. Post-hoc Tukey-Kramer tests showed that higher modularity values were prevalent in state 2 (t=2.446 $p = .014$; state1 M = 0.12, SD = 0.09; state 2 M = 0.17, SD = 0.15) and higher average strength was prevalent in state 1 (t=2.268 $p = .023$; state1 M = 32.37, SD = 10.45; state 2 M = 27.51, SD = 14.77). So, across both music conditions, state 1 was characterized by higher overall connectivity, and state 2 was characterized by more modularity. Increased processing demands such as during listening to A. Webern was related to a more integrated and overall connected brain state as participants spent more time in state 1 when listening to A. Webern than when listening to J.S. Bach.



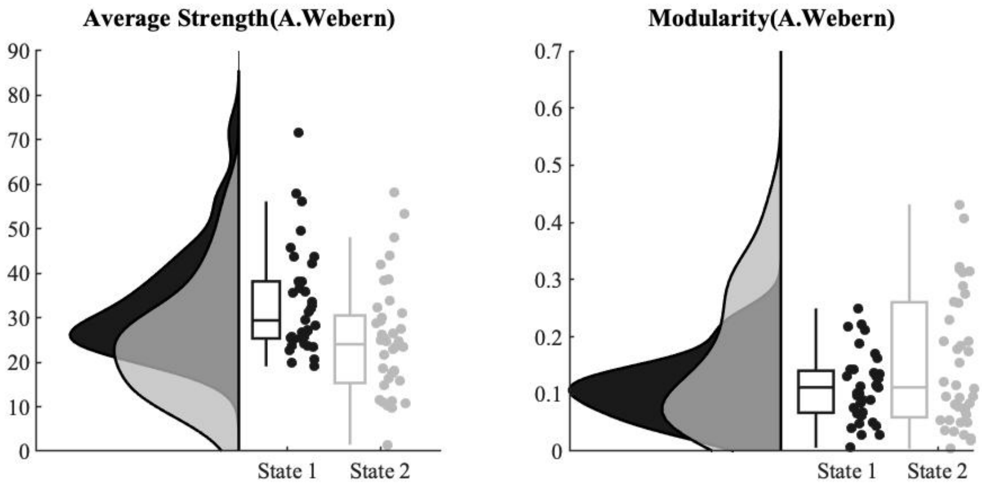


Figure 8. Graph measures computed on the brain states from dynamic functional connectivity analysis across both listening conditions (upper row) and for each listening condition separately (middle & lower row). Across both listening conditions (upper row), the two states differed in modularity and average strength, with the second state exhibiting significantly higher modularity and the first state significantly higher average strength, indicative of higher overall connectivity. Graph measures distributions are shown as raincloud plots (Allen et al., 2019) and boxplots with medians and 95% CI with whiskers representing second and 98th percentiles. Each dot represents a single subject. Asterisks indicate significant effect at $p < .05$. Exclusion of individual values in the modularity index (upper row) and average strength (upper row) that exceeded 2 SDs still resulted in a significant difference at $p = .04$ for modularity index and $p = .014$ for average strength.

We used paired *t*-tests to compute differences between the two listening conditions for three state metrics, namely transition number, dwell time, and frequency. We found that the average number of state transitions differed significantly between the two listening conditions, $t(39) = 3.134$, $p = .033$, Cohen's d = 0.55, with more transitions occurring during listening to the piece by A. Webern (M = 3.02, SD = 1.8) in comparison to the piece by J.S. Bach (M = 2.05, SD = 1.67). The mean dwell time each participant spent in each state during the two listening conditions differed significantly for the second state, exhibiting higher modularity, $t(39) = 3.712$, $p < .001$, Cohen's d = 0.5, where participants seemed to spend more time during listening to the piece by J.S. Bach (M = 18.01, SD = 11.4) in comparison to during listening to the piece by A. Webern (M = 12.48, SD = 10.09), but it did not differ for the first state, exhibiting higher connectivity, ($t(39) = 0.6383$, $p=.52$; listening to the piece by J.S. Bach M=8.5, SD=6.8; listening to the piece by A. Webern M=7.6, SD=5.9). Finally, the frequency with which each participant visited each state differed significantly between the two states, with the first state being visited more frequently during listening to the piece by A. Webern ($t(39) = 1.954$, $p = .05$; A. Webern condition: M = 0.42, SD = 0.2; J.S. Bach condition M = 0.33, SD = 0.22) and the second state being visited more frequently during listening to the piece by J.S.

Bach ($t(39) = 1.954$ $p = .05$; A. Webern condition: M = 0.57, SD = 0.2; J.S. Bach condition M = 0.66 SD = 0.29; see Figure 9).

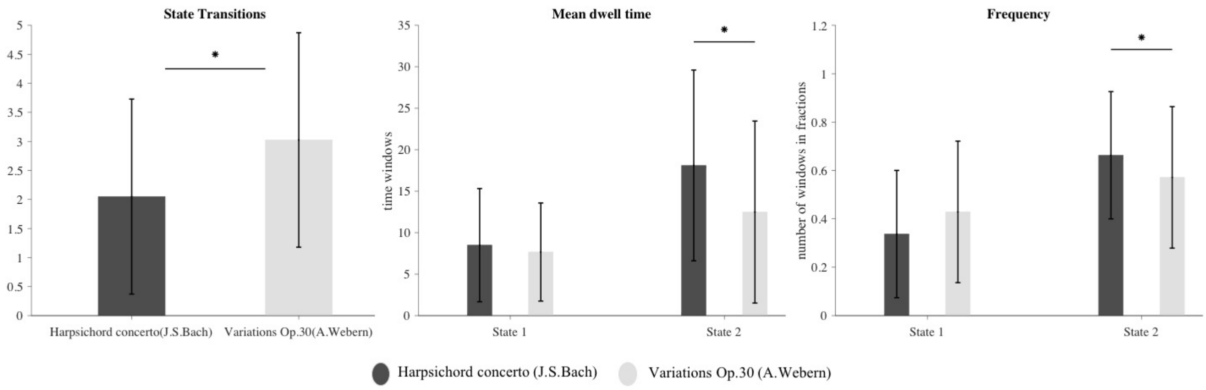


Figure 9. State metrics computed on the dynamic functional connectivity analysis across both listening conditions. During listening to the piece by A. Webern, there was a significant higher number of state transitions in comparison to listening to the piece by J.S. Bach. Participants spent significantly more consecutive time in the second state while listening to the piece by J.S. Bach and spend on average more time in state 1 while listening to the piece by A. Webern. Whiskers in the state metrics indicate standard deviation. Asterisks indicate significant effect at $p < .05$.

Expertise-related neural differences in listening to music

Global graph measures on static functional connectivity

To assess expertise-related differences in music listening, we performed a static functional connectivity analysis for each participant in each listening condition, and then computed two global graph measures, namely average strength and global efficiency. In the condition of listening to the piece by A. Webern, we found significant expertise differences in global efficiency ($t(38) = 1.9451$, $p = .05$, Cohen's d = 0.62; aspiring professionals M = 0.52, SD = 0.1; amateur musicians M = 0.4, SD = 0.09) but no significant expertise differences in average strength ($t(38)= 1.9206$, $p = .06$, Cohen's d=0.62; aspiring professionals M = 50, SD = 14.9; amateur musicians M = 40, SD = 14.6; see Figure 5), even though the effect size was identical. In contrast, in the condition of listening to the piece by J.S. Bach, we found no significant group differences in the measures of global efficiency (*Mann-Whitney* =140, $p = .15$, Cohen's $d = 0.2$; aspiring professionals M = 0.51, SD = 0.16; amateur musicians M = 0.46, SD = 0.13) and average strength (*Mann-Whitney* = 149, $p = .24$, Cohen's $d = 0.2$; aspiring professionals M = 48.46, SD = 22.03; amateur musicians M = 41.82, SD = 18.72).

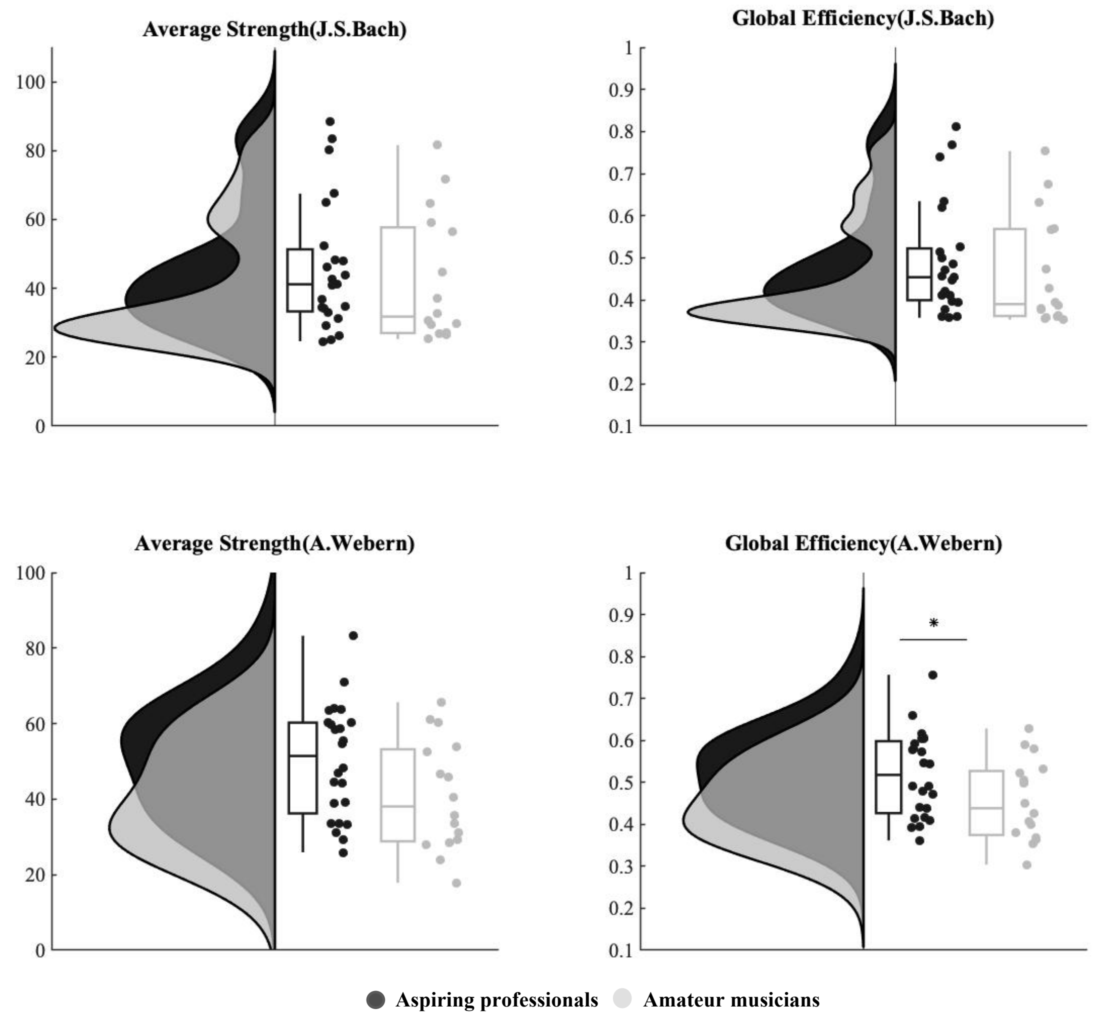


Figure 10. Group comparisons of graph measures network strength and global efficiency for the two listening conditions. In the J.S. Bach condition (upper row) there were no group differences for average strength and global efficiency. In the A. Webern condition (lower row), the group of aspiring professionals (in black) showed significantly greater global efficiency than amateur musicians (in grey). Group distributions are shown as raincloud plots (Allen et al., 2019) and boxplots with medians and 95% CI with whiskers representing second and 98th percentiles. Each dot represents a single subject. Asterisk indicates a significant group differences effect at $p \leq .05$.

Nodal graph measures on static functional connectivity to assess hubs and connector hubs

In addition, we computed two nodal measures: nodal degree as in indicator of nodes acting as hubs, and participation coefficient as an indicator of nodes facilitating communication between communities. In the condition of listening to the piece by A. Webern, we found significant expertise-related differences for the measures of degree and participation coefficient in an extended collection of regions throughout the brain, namely regions of the temporal lobe like the superior temporal gyrus (STG), the inferior (ITG) and middle temporal gyrus (MTG) and the planum polare, frontal and parietal regions like the inferior and middle frontal gyrus, the frontal pole, the parietal and frontal operculum and the insula, lateral occipital cortex, as well as nucleus accumbens (see Table 4). In all these regions, the group of aspiring professionals exhibited higher values, and there were no regions in which the group of amateur musicians had higher degree. In the condition of listening to the piece by J.S. Bach, there were only two regions with expertise-related differences in the measure of degree in the left and right caudate, again such that the group of aspiring professional musicians had higher values than the amateur musicians, and four regions in which the two groups differed significantly in the measure of participation coefficient, again with higher values for the group of aspiring professional musicians, namely the bilateral inferior frontal gyrus, the anterior part of the right temporal fusiform gyrus and the right temporal occipital fusiform gyrus (see Table 4). Paired *t*-tests for within group differences for the measure of degree between the two listening conditions detected regions that differed significantly only for the group of aspiring professional musicians, with higher degree occurring for the condition of listening to the piece by A. Webern (see Table 4). In sum, we found no expertise-related differences in the processing of the supposedly less demanding musical piece by J.S Bach, but found higher global efficiency in aspiring professional musicians during the more challenging listening condition. In addition, the group of higher expertise utilized a wide range of brain regions as hubs and connector hubs during the demanding listening condition and switched to a subset of those regions during the less demanding listening condition.

condition- group comparison	**graph measure**	**brain regions**	
listening to A. Webern aspiring professionals > amateur musicians	degree	frontal lobe	*right middle frontal gyrus,* *right frontal operculum,* *left precentral gyrus,* *right inferior frontal gyrus-pars triangularis,*
		temporal lobe	*left & right posterior inferior temporal gyrus,* *right posterior superior temporal gyrus,*
		parietal lobe	*left parietal opercular cortex,* *right posterior supramarginal gyrus,* *right angular gyrus,*
		occipital lobe	*left lateral superior occipital cortex,* *right paracingulate gyrus,* *left cuneus,* *left supracalcarine gyrus,*
		insular lobe	*left insula,*
		subcortical structures	*right thalamus,* *right caudate,*

			left putamen, *right accumbens*
listening to A. Webern aspiring professionals > amateur musicians	participation coefficient	frontal lobe temporal lobe occipital lobe insular lobe subcortical structures	*left & right frontal pole,* *left middle frontal gyrus,* *left & right inferior frontal gyrus-pars triangularis,* *right posterior superior temporal gyrus,* *left posterior inferior temporal gyrus,* *left planum polare,* *right temporal fusiform cortex-posterior division,* *left superior lateral occipital cortex,* *right inferior lateral occipital cortex,* *left & right insula,* *right paracingulate gyrus,* *right posterior parahippocampal gyrus,* *right caudate*
listening to J.S Bach aspiring professionals > amateur musicians	degree	subcortical structures	*left & right caudate*
listening to J.S Bach aspiring professionals > amateur musicians	participation coefficient	frontal lobe temporal lobe	*right inferior frontal gyrus-pars triangularis,* *right inferior temporal gyrus-anterior division,* *right temporal fusiform cortex-anterior division,* *right temporal occipital fusiform cortex*
listening to A. Webern > *listening to J.S. Bach* aspiring professionals	degree	frontal lobe temporal lobe	*right inferior frontal gyrus-pars triangularis,* *right inferior frontal gyrus-pars opercularis,* *left posterior middle temporal gyrus,* *left & right temporooccipital middle temporal gyrus,* *left & right posterior inferior temporal gyrus,* *right temporooccipital inferior temporal gyrus,* *right posterior supramarginal gyrus,* *right temporal fusiform cortex,* *left temporal occipital fusiform cortex*

Table 4. Brain regions significantly different between the two groups (rows 1- 4) for the nodal measures of degree and participation coefficient for each listening condition. Aspiring professionals had higher degree and participation coefficient values in comparison to the group of amateur musicians. Regions reported at a threshold $p < .05$, following FDR-correction. In row 5, brain regions that differ significantly between listening conditions within the group of aspiring professionals, for the measure of degree. Higher degree values for these regions occurred during listening to the piece by A. Webern. Again, regions reported at a threshold $p < .05$, following FDR-correction.

5.4 Discussion

In this study, we identified and characterized prominent network configurations, referred to as brain states, during unconstrained listening to music. To this end, we used one piece by J.S. Bach, a piece representative of baroque music, and one piece by A. Webern, part of the movement of compositional innovations of the 20th/21st century and belonging to the

2^{nd} Viennese School. We investigated differences in functional organization between the two listening conditions and between expertise groups while listening to the two musical pieces, with dynamic functional connectivity analysis and graph theoretical measures. The two musical pieces differed in metrics of tonality, rhythm and self-similarity, reflecting the different compositional styles of each piece, which translate into listening experiences of different perceptual and cognitive demands. We found that during listening to the piece by A. Webern, participants spent more time in a state characterized by higher average strength and less modularity in comparison to when listening to the piece by J.S. Bach. Further, we sought to assess how musical expertise modulates whole brain network organization. We therefore used graph-theoretic measures applied to static functional connectivity analysis to compare the two groups of participants differing with respect to their training intensity and aspirations: a group of aspiring professional musicians and a group of amateur musicians. We found no expertise-related differences in the processing of the musical piece by J.S. Bach, but found higher global efficiency in aspiring professional musicians during the more challenging listening condition of the piece by A. Webern. In addition, the group of higher expertise showed a wide range of brain regions acting as hubs and connector hubs during the demanding listening condition and switched to a subset of those regions during the less demanding listening condition.

We described the two musical pieces by means of music information retrieval methods (MIR), focusing on tonal, rhythmic and self-similarity measures. As expected, the piece by J.S. Bach had an unequal distribution of pitches along the chromatic scale in comparison to the piece by A. Webern, where the use of chromatic pitches was distributed more uniformly. Furthermore, the piece by J.S Bach was characterized by higher key and pulse clarity as well as higher self-similarity over time in its frequency spectrum, indicating higher repetition of frequency patterns. These findings highlight the differences in the compositional style of the two pieces: the piece by J.S. Bach belongs to the "baroque music" genre and displays more distinct tonal and rhythmic hierarchies as well as higher self-similarity in the frequency spectrum, while in contrast the piece by A. Webern belongs to the "contemporary classical music" genre of the 2^{nd} Viennese School of music and displays the compositional innovations of this movement on tonal aspects, treating all twelve tones within an octave as equivalent, on rhythmic aspects of complex and varied rhythms without a clear metrical structure, and lower self-similarity in the frequency spectrum, suggestive of reduced acoustic predictiveness, especially for inexperienced listeners. Evidently, these two musical pieces evoke very different listening experiences. Music by J.S. Bach is typically more familiar and enculturated for Western listeners, following tonal and metrical hierarchies within the Western musical tradition, aspects shown to modulate predictive and expectancy processes as well as to evoke emotional states, reward and pleasure sensation in relation to processing of musical stimuli (Koelsch et al., 2019; Mencke et al., 2019). On the other hand, music by A. Webern presents a challenging musical experience. The lack of tonal and metrical hierarchies and regularities do not offer an auditory and cognitive reference point (Rosch, 1975), and hinder grouping mechanisms that would facilitate processing and play a central role in formation of predictions (Mencke et al., 2019). Music, without tonal center, is also characterized by high entropy and low information content (Dean & Pearce, 2016), creating an experience of 'predictive uncertainty' (Hansen & Pearce, 2014), complexity and ambiguity (Mencke et al., 2019). These characteristics have perceptual and cognitive implications reflected in lower performance on various measures, as has been shown in studies using stimuli with tonal and atonal features, including memory performance during melody recollection, melodic transposition, processing speed, detection of pitch deviant and generation of expectations (Mencke et al., 2019, 2021). Nevertheless or maybe even more so, contemporary-classical music such as by A. Webern stimulates aesthetic experiences modulated by familiarity and exposure to this genre of music (Dean & Pearce, 2016; Omigie et al., 2017), as well as by other factors, including "aesthetic framing" (Brattico et al., 2013), openness to experience (Nusbaum & Silvia, 2011), cognitive mastering (Leder et al., 2004) and processing fluency (Reber et al., 2004), in the case of musically expert listeners. Furthermore, it has the potential to evoke pleasure and reward sensations resulting from decoding perceptual uncertainties, stimulating curiosity and exploration of novel acoustic experiences (Gold et al., 2019; Mencke et al., 2019, 2021).

In the dynamic functional connectivity analysis, two states emerged capturing whole brain organization underlying the processing of the two musical pieces, one with overall occurrence of approximately 38% of the time, characterized by higher overall connectivity, and one with higher occurrence (68%), characterized by higher segregation, as indicated by the modularity index. During listening to the piece by A. Webern, more between-state transitions occurred and participants appeared to spend more time in the first state with higher overall connectivity. While listening to the piece by J.S. Bach, participants spent more continuous time in the second state with higher segregation. These findings can be understood within a research framework which views the brain as a dynamic network which continuously reconfigures on both spatial and temporal scales, interchanging between states of higher integration and segregation, promoting adaptation to changing environmental and neural demands across task states and in resting state (Alavash et al., 2016; Allen et al., 2014; Betzel et al., 2016; Cole et al., 2013; Sporns, 2013; Tognoli & Kelso, 2014). The differences in overall connectivity and modularity of the states and the differences in state metrics are taken to reflect the different processing demands that the two musical pieces pose. The finding that during listening to A. Webern participants spend more time in the state characterized by higher overall connectivity, is in line with evidence showing that integrated states arise more in situations where greater cognitive effort is required in order to achieve effective behavioral performance (Kitzbichler et al., 2011). More integrated states are hypothesized to facilitate adaptability and performance on cognitive tasks while decreases of brain modularity have been observed in the presence of greater task demands (Vatansever et al., 2015). The level of network integration has additionally been shown to be modulated by task demands (Shine et al., 2016). The reversed pattern of brain configurations with higher modularity is observed in easier tasks, requiring less network integration (Cohen & D'Esposito, 2016), or reflecting more automatic/habitual processing (Shine & Poldrack, 2018). Changes in the modularity of brain networks has been shown to take place, for example, in the course of training in motor tasks (Bassett et al., 2011, 2015). The higher transition number between states during listening to the piece by A. Webern can be understood as indicative of the effortful processing that evokes more state switching, which is considered a means to explore different brain states – so to speak the brain's dynamic repertoire (Deco et al., 2011) – in order to facilitate and enhance effortful processing, moving from more local and modular configurations of sensory processing to more integrated states enabling complex cognition (Sadaghiani et al., 2015). On the other hand, the higher mean dwell time for the more modular state while listening to J.S. Bach can be interpreted to suggest lower processing demands, requiring less integration of brain regions throughout the brain (Cohen & D'Esposito, 2016)

Further, we investigated expertise-related differences in whole brain organization using graph measures applied to static functional connectivity analysis. In the condition of listening to the piece by A. Webern, we found the group of aspiring professionals to exhibit significantly higher global efficiency than the group of amateur musicians. This finding emphasizes that aspiring professional musicians exhibit overall a more integrated network configuration which facilitates processing in the more demanding condition. This finding is in line with other studies showing musicians to exhibit higher indices of whole brain degree, density, strength, and global efficiency in tonal processing of music (González et al., 2021; Paraskevopoulos et al., 2017), as well as clustering coefficient (Leipold et al., 2021). The absence of expertise-related differences in graph measures in the condition of listening to the piece by J.S. Bach may not be too surprising in light of evidence of higher response similarity in listening to familiar music, as assessed by intersubject correlation analysis, regardless of expertise status (Madsen et al., 2019), along with evidence of overlapping brain response patterns of professional and amateur musicians in a paradigm using tonal sequences containing different degrees of structural irregularities, especially in trials of low difficulty (Oechslin et al., 2013). It might indicate that in the less effortful processing condition there was no need for utilizing additional functional resources to assist processing.

The analysis of the nodal measures and the investigation of the between-group differences in regions acting as hubs and connector hubs follows up on previous findings showing that groups with different expertise utilize different regions as hubs during musical processing (Alluri et al., 2017; Loui et al., 2012). Here, the group with higher expertise, namely aspiring professional musicians exhibited higher degree and participation coefficient in a wide range of regions, especially during the challenging musical condition. The group of amateur musicians did not have higher degree or participation coefficient in any regions in comparison to the group of aspiring professional musicians. We consider this to be indicative of an overall higher flexibility in network organization for the group of aspiring professionals, with changes in functional connectivity and communication among different subnetworks being adaptive to the demands posed by the listening condition. Relevant evidence in the literature suggests that flexible hub connectivity patterns facilitate adaptive novel task performance and that changes in community interactions are modulated by task demands (Cole et al., 2013). Furthermore, higher variability in the connectivity between networks has been associated with higher cognitive flexibility (Douw et al., 2016).

The regions where aspiring professional musicians exhibit higher degree and participation coefficients in comparison to amateur musicians during listening to the piece by A. Webern are repeatedly reported for their prominent role in auditory processing. Regions of the temporal lobe, like the superior temporal gyrus (STG), the inferior (ITG) and middle temporal gyrus (MTG) and the planum polare, here as nodes of higher degree and participation coefficient, are considered core auditory processing regions in relation to various aspects of musical processing (Koelsch, 2011). Higher degree, clustering, and local efficiency, especially for the left STG, has been reported in musicians with absolute pitch compared to musicians without absolute pitch during listening to musical clips (Loui et al., 2012). Higher nodal degree has been found for musicians in cerebellar regions, the right temporal pole, the inferior temporal gyrus and the parahippocampal gyrus (Alluri et al., 2017), which we found as a connector hub for musicians while listening to music by A. Webern. Activity in the right superior temporal gyrus (rSTG) alongside the pars opercularis of the right inferior frontal gyrus and bilaterally the anterior cingulate and paracingulate gyrus, regions here reported as hubs and connector hubs, have been shown to best discriminate between musicians and nonmusicians (Saari et al., 2018).

Frontal and parietal regions implicated as hubs and connector hubs in aspiring professionals while listening to Webern, like the inferior and middle frontal gyrus, the frontal pole, the parietal & frontal operculum and the insula, have been associated with cognitive aspects of musical processing and integration of multi-sensory information. Activity in frontal and posterior parietal regions, including the pre-supplementary motor area, the dorsolateral and rostrolateral prefrontal cortex, the intraparietal sulcus and the precuneus, has been found to be modulated by exposure to chromatic music, diatonic music and atonal sequences before, in a cohort of participants with excellent relative pitch (Li et al., 2021). The frontal operculum, part of a network including lateral prefrontal cortices, has been found to facilitate cognitive control and drive attentional resources to relevant stimuli and to link auditory, somatosensory, and motor cortical areas as a connector hub (Quirmbach & Limanowski, 2022). Musicians, in comparison to nonmusicians, have been shown to exhibit increased functional connectivity of the parietal operculum with Heschl's gyrus, planum temporale, the precentral and postcentral gyrus (Tanaka & Kirino, 2018). Inferior frontal regions like the pars triangularis and opercularis are known for their role in language and musical syntactic processing as well as processing and integration of sequential information over time (Tillmann et al., 2006). Activity in the inferior frontal gyrus, as mentioned earlier, was also found to discriminate between musicians and nonmusicians (Saari et al., 2018). The insula is a hub linking several large scale networks (Gogolla, 2017) and serves a wide variety of functions ranging from sensory and affective processing, also in relation to music (Koelsch et al., 2021), to high-level cognition and interoceptive processes (Uddin et al., 2017; Zamorano et al., 2017). The insula alongside the anterior cingulate cortex have been reported to exhibit increasing node degree for decreasing onset ages of musical training (Zamorano et al., 2017) and musicians are shown to have increased functional connectivity in comparison to nonmusicians in an insula-based network including anterior and middle cingulate cortex (Zamorano et al., 2017).

Regions identified as hubs and connector hubs in both the A. Webern and the J.S. Bach condition for aspiring professional musicians, namely the temporal occipital fusiform cortex, the anterior fusiform cortex and lateral occipital cortex, are considered centers of multisensory integration, and have been associated with musical notation reading and processing aspects of musical richness (Satoh et al., 2015). The fusiform gyrus together with the amygdala and anterior superior temporal gyrus have additionally been reported as a network for emotion-related processing during music listening (Pehrs et al., 2014). The nucleus accumbens, exhibiting higher degree for aspiring professionals in the condition of listening to A. Webern, is known as a hub of reward and music enjoyment-related activity (Gold et al., 2019), arising from the interaction between mesolimbic reward circuitry and cortical networks involved in perceptual analysis and valuation (Salimpoor et al., 2013). Activity in the nucleus accumbens and its connectivity patterns have also been associated with music-induced pleasantness in relation to musical surprises (Shany et al., 2019). The caudate nucleus reported here bilaterally as the only regions where aspiring professional musicians exhibited higher degree during listening to J.S. Bach, is part of the basal ganglia, involved both in emotion and rhythm processing in relation to music perception (Pando-Naude et al., 2021) and is known to be recruited in rhythmic entrainment (Kokal et al., 2011; Trost et al., 2014). Caudate is also suggested to be part of a thalamocortical system for integration of rhythmic and tonal information (Musacchia et al., 2014).

Altogether, the aspiring professional musicians in comparison to the amateur musicians appear to utilize brain regions alongside the dorsal and ventral auditory streams as well as higher-order associative regions, for perceptual, cognitive, emotional and reward-related musical processes, especially in the challenging auditory condition. In addition, they also appear to exhibit more efficient communication between subnetworks dedicated to different aspects of these processes. Effects of musical style in functional connectivity were also reported in a recent study, where cellists played baroque and contemporary music (González et al., 2020). Apart from common activation of motor and sensory regions in both conditions, playing baroque music was associated with connectivity among Heschl's gyrus and superior frontal gyri, planum temporale and caudate nucleus, while playing contemporary music was exclusively associated with connectivity in cerebellar-vermis, insular cortex and parietal operculum (González et al., 2020). Lastly, it is worth mentioning that many of the regions reported here are shown to be essential information and communication hubs, regardless of the context of music processing and musical expertise (Deco et al., 2021; GeethaRamani & Sivaselvi, 2014; Zhao et al., 2019).

Finally, we would like to address some of the limitations of the current study. First of all, regarding the dynamic functional connectivity analysis, the choice of window length is a determining factor for the tradeoff between precision and temporal resolution. Too short time windows can induce spurious fluctuations and increased noise sensitivity, while too long window sizes can hinder the detection of temporal variations of interest (Preti et al., 2017) and a given window size might not capture reconfigurations of brain networks developing on different time scales (Lurie et al., 2019). However, empirically, window sizes between 30s and

60s appear to yield robust results in dynamic FC analysis (Shine & Poldrack, 2018), which also guided our decision for a window size of 60s, also in relation to the experimental paradigm of unconstrained listening to music without examining specifically the relation between dynamic functional connectivity and specific acoustic features with precise temporal occurrence. Furthermore, using pairwise Pearson's correlation is only one of the possible ways to uncover relationships between brain regions and does not capture all aspects of functional brain organization (Preti et al., 2017). K-means clustering, used here to uncover states based on dynamic FC is only one of the existing methods, including hierarchical clustering and hidden Markov models and there is no consensus yet on which one is the optimal choice for different occasions (Preti et al., 2017). Subjects are allowed to be only in a specific state at a given point in time, while multiple states might be present at a given point in time to varying degrees. The modularity index, computed here using maximization of the modularity function, partitions a network into a set of communities in a nondeterministic way and produces many near-optimal partitions of the network (Bassett & Gazzaniga, 2011; Sporns & Betzel, 2016). Hub detection can be done using numerous different graph measures, most of which express aspects of node centrality, including degree, closeness centrality, eigenvector centrality and betweenness centrality, and not one of them is necessary and sufficient for exhaustive hub detection (van den Heuvel & Sporns, 2013) while they might yield slightly differentiated results, although different metrics are often found to be highly correlated (Zhao et al., 2019). In our case, the choice of the measure of degree was to assist and simplify interpretation and is in no way meant as an exhaustive description. Additionally, degree was computed on the whole brain network, and not within each region's community in order to compute within group comparisons for the group of aspiring professionals between the two listening conditions. Furthermore, within the group aspiring professional musicians there was a wide variety of primary instruments of practice, which results in inhomogeneity in their expected experience with specific kinds of music. Potentially, focusing on specific groups of instrumentalists would be more conclusive in order to understand how expertise shapes brain architecture in challenging auditory conditions (González et al., 2020). Musical features of difference between the pieces are not time-locked to the neural signals captured by the fMRI and thus specific occurrences of such features cannot be directly linked to the brain states. Finally, we have no information on participants' familiarity, exposure and aesthetic appreciation of the two musical pieces, which would facilitate further analysis associating these aspects with dynamic and static functional connectivity metrics and would further assist interpretation of results. We might speculate that more participants within the group of aspiring professional musicians might have been exposed to contemporary classical music of the 2nd Viennese School, while attending their preparatory courses, as part of a more elaborate curriculum in music studies than participants of the amateur musicians group.

5.5 Conclusion

In this study, we investigated how processing demands posed by two musical pieces of different compositional styles and genres are reflected in whole-brain configurations. We found that increased processing demands related to a more integrated and overall connected brain state. Further, we looked for expertise-related differences in functional organization during listening to the two musical pieces and found the group of aspiring professional musicians to exhibit higher global efficiency than the group of amateur musicians in the challenging listening condition. In addition, the group of higher expertise utilized a wide range of brain regions as hubs and connector hubs during the demanding listening condition and switched to a subset of those regions during the less demanding listening condition. These findings highlight that whole-brain configurations are modulated by processing demands and indicate the effect of expertise on efficient network reconfigurations according to the demands posed.

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6 Study III: Observing plasticity of the auditory system: Volumetric decreases along with increased functional connectivity in aspiring professional musicians

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6.1 Introduction

Playing a musical instrument is an intense, multisensory experience. As music itself is a highly complex stimulus and musicians typically devote a lot of time to their training, they offer an excellent model for studying experience-dependent plastic changes in the brain. Music expertise has served as a particularly rich and fruitful domain for investigating plastic changes. It involves several sensory systems and the motor system, and it poses high demands on cognitive control processes (Herholz & Zatorre, 2012; Jäncke, 2009; Münte et al., 2002; Gottfried Schlaug, 2015). Most of the available data on the association between music expertise and the brain are cross-sectional rather than longitudinal. Musicians typically show an enlargement of brain areas associated with music-related processes in the auditory, motor, and visuospatial domain (Bermudez et al., 2009; Gaser & Schlaug, 2003; Hutchinson et al., 2003; James et al., 2014; Schneider et al., 2002). Several brain areas, including the auditory cortices, the anterior corpus callosum, the primary hand motor area and the cerebellum, differ in their structure and size between musicians and control subjects (Münte et al., 2002) and these volumetric differences have been shown to be of behavioral relevance (Foster & Zatorre, 2010; Hyde et al., 2009; Schneider et al., 2002). Groussard and colleagues (Groussard et al., 2014) have identified regions in the brain that increased in volume with the duration of practice, namely left hippocampus, right middle and superior frontal regions, right insula and supplementary motor area, left superior temporal and posterior cingulate areas. Interestingly, while in some regions changes in volume seem to have occurred during early stages of musical training, like in left hippocampus and right middle and superior frontal areas, changes in other areas, specifically in left posterior cingulate cortex, superior temporal areas and right supplementary motor area and insula, were more pronounced or even only occurred after several additional years of practice (Groussard et al., 2014). Similarly, James and colleagues have sorted music expertise into three levels to investigate its influence on grey matter density (James et al., 2014). While they found grey matter increases with expertise in areas implicated in working memory and attentional control, that is in fusiform gyrus, mid orbital gyrus, inferior frontal gyrus, intraparietal sulcus, cerebellum, and Heschl's gyrus, they detected grey matter decreases with expertise in areas related to sensorimotor function, namely in perirolandic and striatal areas.

Arguably, musicians brains do not only differ structurally from nonmusicians but show also functional differences, such as strengthened functional coupling among relevant regions while performing musical tasks (Herholz & Zatorre, 2012). Indeed, numerous functional imaging studies have compared musicians and nonmusicians and have observed differences in activity across many brain regions when individuals were performing musical tasks involving discrimination (Foster & Zatorre, 2010; Koelsch et al., 2005), working memory (Gaab et al., 2006), or production (Bangert et al., 2006; Kleber et al., 2010). Despite the many differences among the tasks used, one area that has been commonly activated in many of these studies was the left superior temporal gyrus, a region that has been linked to musical training in terms of cumulative practice hours (Ellis et al., 2012). Of interest, fMRI studies of perceptual learning with pitch tasks have resulted in both increases (Gaab et al., 2006) and decreases (Jäncke et al., 2001) of activity in auditory areas. Similarly, training to discriminate between melodies constructed of increasingly smaller intervals well below a semitone has been shown to be accompanied by general activation decrements in auditory regions, along with activation increases in frontal cortices (Zatorre, Delhommeau, et al., 2012). Before training, the data had shown the expected dose-response function of more activity with increasing microtonal pitch interval size. After training, however, there was a reduction in blood oxygenation in response to increasing interval size (Zatorre et al., 2012), suggesting that learning might decrease the number of neuronal units that are needed to perform the task (Makino et al., 2016; Poldrack, 2000).

The brain exhibits spontaneous and systematic activity during wakeful rest (Biswal et al., 1995; van den Heuvel & Hulshoff Pol, 2010; Zuo & Xing, 2014). Exploiting this characteristic, one can compute resting-state functional connectivity which is based on spontaneous low-frequency fluctuations (< 0.1 Hz) in the blood oxygen level-dependent signal (Biswal et al.,1995), and uncover functional networks that consist of brain regions frequently working together. Activity in the resting state may therefore reflect the repeated history of coactivation within or between brain regions for efficient task performance (Baldassarre et al., 2016; Cole et al., 2012, 2014, 2016; Ventura-Campos et al., 2013). Only a few studies have investigated differences in functional connectivity as a function of musical training. Pianists were found to show greater functional connectivity between left auditory cortex and the cerebellum than control participants (Luo et al., 2012). Regions with increases in grey matter in musicians compared to nonmusicians located in posterior and middle cingulate gyrus, left superior temporal gyrus and inferior orbitofrontal gyrus have been shown to have increased connectivity to right prefrontal cortex, left temporal pole, left premotor cortex and supramraginal gyri (Fauvel et al., 2014). Palomar-García and colleagues tested for differences between musicians and nonmusicians in auditory, motor, and audiomotor connectivity and found stronger connectivity between right auditory cortex and right ventral premotor cortex, which correlated with years of practice (Palomar-García et al., 2017). They also found reduced connectivity between motor areas that control both hands in those musicians whose instrument required bimanual coordination, and increased volume in right auditory cortex. This increased grey matter volume correlated negatively with age at which training had begun and was related to increased connectivity between auditory and motor systems (Palomar-García et al., 2017).

As summarized above, most studies on neural correlates of music expertise rely on cross-sectional comparisons, rendering conclusions of whether observed group differences were pre-existing or the result of learning de facto impossible. It has been impressively shown, though, that monozygotic twins, i.e. with identical genes, differing on musical training do indeed exhibit neuroanatomical differences, thereby providing strong support for the causal effects of training (Manzano & Ullén, 2018). Still, longitudinal studies with observations within the same individuals over time provide the most direct evidence for effects of musical training on neuroanatomy. We therefore used a variety of methodologies to characterize within-person changes *over time* in aspiring professionals intensely preparing for an entrance exam at a University of the Arts and compared these to skilled amateur musicians not preparing for a music exam. Specifically, we used anatomical MRI along with resting-state fMRI to investigate structural changes in grey matter volume that arise during this intense learning period within individuals over time and to analyze the changes in functional interactions that accompany these structural changes. We hypothesized that (1) in comparison to amateur musicians, aspiring professional musicians will show volumetric changes in regions previously identified to be relevant in the context of musical training, especially auditory cortex, (2) the regions of structural change will exhibit increased functional connectivity to other regions related to the auditory network, specifically, temporal regions, motor regions, and cingulate gyri and (3) these changes in structure and functional connectivity will be related to behavioral performance.

6.2 Material and methods

<u>Participants</u>

Information about the participants recruited can be found in detail in subsection 4.2 (chapter 4), as all three projects of this dissertation are based on data acquired from the same longitudinal study.

<u>Experimental Design</u>

Participants were invited for behavioral testing as well as magnetic resonance imaging (MRI) assessment between one to five times, depending on their availability, in the course of about a year, with approximately 10-12 weeks distance between appointments (see Figure 11).

Participants were put in the MR scanner for about an hour and 15 min, and were then tested on the in-house developed "Berlin Gehoerbildung Scale" (Lin et al., 2022), a test to assess music aptitude at expert levels.

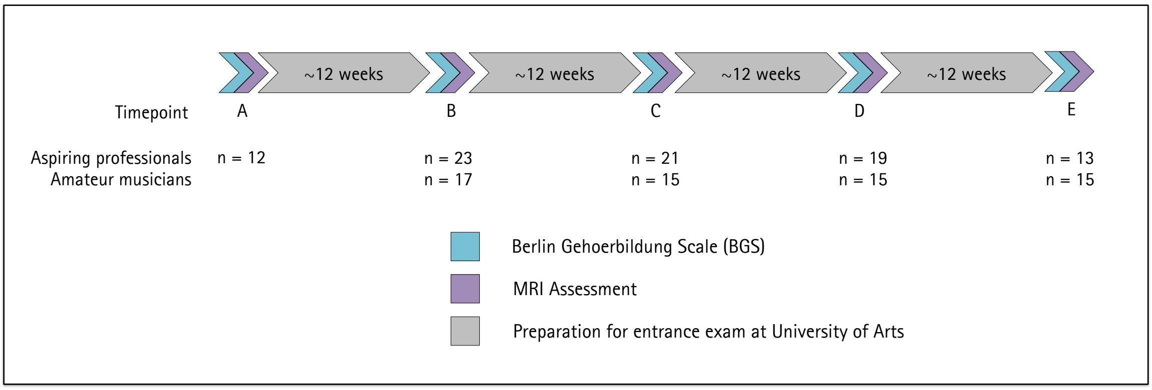


Figure 11. Overview of experimental design with recruitment numbers for aspiring professionals and amateur musicians at each timepoint.

Behavioral Measure of Music Expertise

The *Berlin Gehoerbildung Scale* (BGS) was designed by André Werner, a composer and collaborator in this study. It is a listening and transcription task focused on assessing music expertise (for a detailed description see Lin et al., 2022). It is informed by music theory and uses a variety of testing methods in the ear-training tradition. Items cover a variety of topics in music theory and ear training, including intervals, scales, dictation, rhythm, chords, cadences, identifying mistakes in music excerpts, and instrument recognition. Using behavioral data of amateur musicians, aspiring professional musicians, as well as 19 music students already studying music at a University of Arts, we have established a hierarchical structural equation model (SEM) of their behavioral performance the first time they encountered the test (Lin et al., 2022). The hierarchical model postulates four first-order factors of musical abilities, namely "Interval and Scales," "Dictation," "Chords and Cadences," and "Complex Listening," which together define a second-order factor of general music expertise. These four first-order factors load highly onto the second-order factor music expertise. We fixed the factor loadings of this established model and then extracted the second-order factor scores for each individual at each time point to investigate changes in performance over time. We then entered the factor scores into a repeated-measures ANOVA with the factors Time (timepoint B, C, and D, as these measurement occasions provide us with the largest sample) and Group (aspiring professionals vs. amateurs).

MRI Data Acquisition

MR images were collected on a Siemens Tim Trio 3T MR scanner (Erlangen, Germany) with a standard 12-channel head coil. The MR measurement protocol included a T_1-weighted structural scan and a resting-state acquisition.

As structural images, we used a three-dimensional T_1-weighted magnetization prepared gradient-echo sequence (MPRAGE) of 9.20 minutes with the following parameters: TR = 2500 ms, TE = 4.77 ms, TI = 1100 ms, flip angle = 7°, bandwidth = 140 Hz/pixel, acquisition matrix = 256 × 256 x 192, isometric voxel size = 1 mm^3. We used the prescan normalize option and a 3D distortion correction for non-linear gradients.

Whole brain functional images were collected using a T_2*-weighted EPI sequence of 8 minutes sensitive to BOLD contrast (TR = 2000 ms, TE = 30 ms, FOV =216 × 216 × 129 mm^3, flip angle = 80°, slice thickness 3.0 mm, distance factor = 20%, voxel size = 3 mm^3, 36 axial slices, using GRAPPA acceleration factor 2). Slices were acquired in an interleaved fashion, aligned to genu-splenium of the corpus callosum.

Structural Data Analysis

The structural MPRAGE images were processed by means of the Computational Anatomy Toolbox (CAT12; v1247; http://dbm.neuro.uni-jena.de/cat/) for SPM12 (v7219; www.fil.ac.uk/spm/) in Matlab 2017a (the Mathworks, Inc., Natick, MA, USA). Using default parameters, pre-processing of the data involved intra-subject realignment, bias-field and noise removal, skull stripping, segmentation into grey (GM) and white matter (WM) and cerebrospinal fluid (CSF), and finally normalization to MNI space using DARTEL to a 1.5 mm isotropic adult template provided by the CAT12 toolbox (whereby normalization is estimated for the mean image of all time points and then applied to all images). The resulting grey matter (GM) maps were smoothed with a standard gaussian kernel of 8 mm full-width at half maximum (FWHM). These GM maps represent voxel-wise information on grey matter probability which is an estimate of grey matter volume in an arbitrary unit (Ashburner & Friston, 2005).

As for quality assurance, images were first visually inspected for artifacts prior to processing. Then, a statistical quality control based on inter-subject homogeneity after segmentation was conducted using the “check homogeneity” function in CAT12. After preprocessing, all images were visually checked again for artifacts, whereby none were detected.

Statistical analysis of the GM maps was first carried out by means of a two-sample *t*-test to test for initial structural differences between aspiring professional and amateur musicians at measurement occasion B (the first timepoint where both groups were fully recruited). This analysis included 23 aspiring professionals and 17 amateur musicians. An absolute grey matter probability threshold of 0.2 was applied. To control for type-I error, a significant effect was reported when the results met a peak-level threshold of $p < 0.005$ and when the cluster size exceeded the expected voxels per cluster threshold ($k > 259$ in this case) in combination with correction for non-isotropic smoothness. The expected voxels per cluster threshold was computed automatically by the CAT12 toolbox according to random field theory and empirically determines the minimum number of voxels that, in combination with a voxel-level threshold, clusters must meet in order to be reported (Hayasaka & Nichols, 2004). In addition, correction for non-isotropic smoothness adjusts the minimum cluster size depending on the local smoothness of the data. This is a common cluster correction method used for whole-brain VBM analyses.

To further characterize pre-existing structural differences in grey matter volume between those two groups of musicians, we additionally performed a region-of-interest (ROI) analysis, focusing on left and right superior temporal gyrus, as well as further divisions into bilateral planum temporale, Heschl's gyrus, and planum polare (taken from the HarvardOxford atlas https://identifiers.org/neurovault.collection:262) (Desikan et al., 2006).

The main analysis in this paper focused on differential changes over time in the two groups of musicians by means of a whole-brain flexible factorial design with a focus on the interaction Time x Group. Since not all participants provided data for all time points, we based our statistical analysis on the middle three measurement occasions (B, C, and D) and only included those participants that contributed data to those three time points since this provided us with the highest possible number of participants for a longitudinal analysis in SPM. This resulted in a final sample of 19 aspiring professionals and 15 amateur musicians in this statistical comparison in which we tested for brain regions that display a significant increase or decrease in aspiring professionals compared to amateur musicians over time.

Again, an absolute grey matter probability threshold of 0.2 was applied. To control for type-I error, here, a significant effect was reported when the results met a peak-level threshold of $p < 0.001$ and when the cluster size exceeded the determined expected voxels per cluster threshold ($k > 47$) in combination with correction for non-isotropic smoothness (as explained above).

To investigate potential relationships between brain volume changes in the clusters showing a significant Time x Group interaction with behavioral performance, we extracted the data from significant clusters using the REX toolbox (region-of-interest extraction tool; The Gabrieli Lab, MIT; http://www.alfnie.com/software), subtracted pretest from posttest values and correlated the difference scores with behavioral performance scores using Pearson's correlation coefficient.

Functional MRI data analysis

Data pre-processing of the resting state data was performed using the toolbox DPABI (v4.0) (Yan et al., 2016) running under Matlab2014b. The first 10 EPI volumes were discarded to allow the magnetization to approach a dynamic equilibrium. All volume slices were corrected for different acquisition times and then realigned. Individual structural images were co-registered to the mean functional image after realignment. The transformed structural images were then segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) (Ashburner & Friston, 2005). To regress out head motion, respiratory and cardiac effects, we used the Friston 24-parameter model (Friston et al., 1996) as well as signals from WM and CSF. In addition, linear and quadratic trends were also included as regressors since the BOLD signal exhibits low-frequency drifts. The DARTEL tool (Ashburner, 2007) was used to normalize the functional data to the Montreal Neurological Institute (MNI) template. We used a spatial filter of 4 mm FWHM and finally performed temporal filtering (0.01–0.1 Hz).

Seed-based functional connectivity analysis

We then conducted an exploratory analysis by means of DPABI computing *functional connectivity maps with a seed region* consisting of left planum polare in MNI space, taken from the Harvard Oxford atlas (Desikan et al., 2006). To do so, the mean time course of all voxels in the seed region was used to calculate pairwise linear correlations (Pearson's correlation) with other voxels in the brain. Individuals' r values were normalized to z values using Fisher's z transformation.

Statistical analysis of the functional connectivity maps was again carried out by means of a whole brain flexible factorial design, focusing on measurement occasions B, C, and D. We entered the images containing the z-transformed correlation values (between the seed region planum polare and all other voxels in the brain) in the second-level analysis with a focus on a time-by-group interaction, using a family-wise error (FWE) correction for multiple comparisons at $p < .05$ (cluster size k = 20 voxels). We used the REX toolbox (region-of-interest extraction tool; The Gabrieli Lab, MIT; http://www.alfnie.com/software) to extract the z-transformed correlation coefficient values from within those clusters showing a significant time-by-group interaction.

Graph Theory Analysis

To perform connectivity analysis using graph-theory measures, we used BRAPH (BRain analysis using GraPH theory) (Mijalkov et al., 2017), a toolbox written in Matlab that uses the Brain Connectivity Toolbox codebase (https://sites.google.com/site/bctnet/) (Rubinov & Sporns, 2010) to calculate network matrices. Such correlation matrices based on *r* correlation values were generated for every subject and then utilized in the calculation of both global and nodal measures. In this framework, nodes are brain regions based on the parcellation of the HarvardOxford atlas (Desikan et al., 2006) and edges represent the correlations between the temporal activation of pairs of brain regions. The constructed matrix is a weighted undirected matrix, where the edges indicate the strength of the connection. As is common practice, only positive values were used in the calculation of nodal and global metrics (negative correlations were set to zero).

We computed five *nodal measures* for the left planum polare including degree, path length, global efficiency, local efficiency, and the clustering coefficient. The degree refers to the total number of edges connected to a node. In the calculations, the weights of the connections were ignored by binarizing the connectivity matrix so that only edges with nonzero weights were considered connected. Path length refers to the average distance from a node to all others. The distance between two nodes is defined as the length of the shortest path between those nodes. In the case of a weighted undirected graph, the length of an edge is a function of its weight. Typically, the edge length is inversely proportional to the edge weight (i.e., a high weight implies a shorter connection). The global efficiency at the nodal level defines the efficiency of the information transfer from one region to the whole network, which assesses the average inverse shortest path length between one node and all other nodes in the network. The local efficiency as a nodal measure is calculated as the global efficiency of the node on the subgraph level, created by the node's neighbors. It reflects the efficiency of the information transfer from each region to the neighboring regions. The clustering coefficient at a nodal level is calculated as the fraction of triangles present around a node and is a measure of segregation. It reflects the ability for specialized processing in small groups of nodes and is thus regarded a measure of local connectedness within a network.

In addition, we computed four *global measures* including all nodes of the whole-brain network, namely characteristic path length, global efficiency, local efficiency and clustering coefficient. The characteristic path length as a global measure is calculated as the average of the path lengths of all nodes. Global efficiency at the global level is the average of the global efficiency of all nodes in the graph and is inversely related to the characteristic path length. Local efficiency computed on the global level is the average of the local efficiencies of its nodes and reflects how well the nodes communicate with adjacent nodes. The clustering coefficient as a global metric is the average of the clustering coefficients of all nodes.

Statistical significance testing was done by extracting the values of the three measurement occasions for local and global measures for each subject from BRAPH and then testing for a time-by-group interaction separately for each nodal and global measure using SPSS, in the end applying a correction for multiple comparisons using the false discovery rate (FDR) algorithm (p-value of .05; https://www.sdmproject.com/utilities/?show=FDR).

6.3 Results

Behavioral results

Based on BGS results, aspiring professional musicians showed significantly higher levels of general music expertise than amateur musicians at measurement occasion B, which corresponds to an early phase of assessment, $t(32) = 4.57$, $p < .001$, Hedges' $g = 1.58$. Furthermore, aspiring professionals showed an increase in performance, whereas amateurs' performance remained relatively stable, as reflected by a significant time-by-group interaction, $F(2,64) = 8.53$, $p = .001$, partial η squared = 0.21.

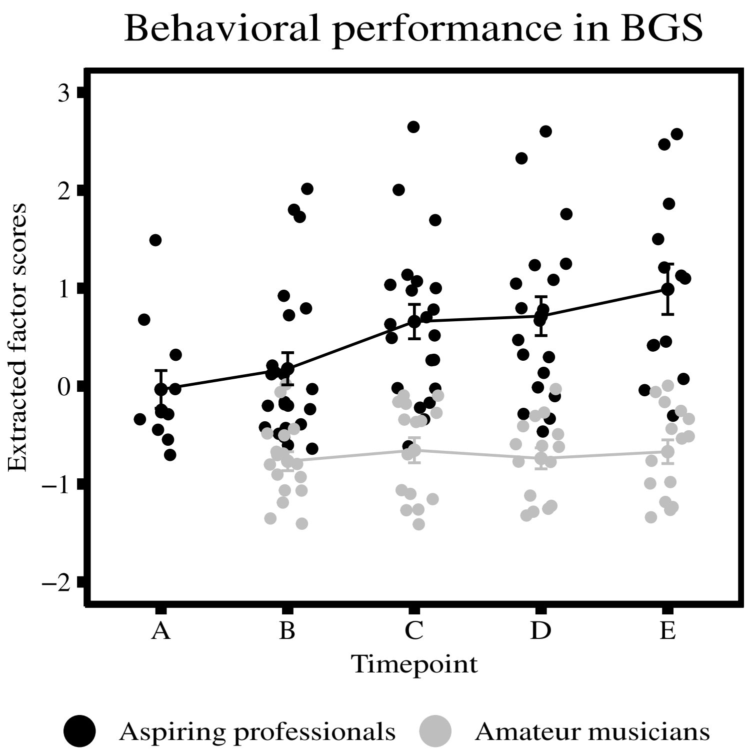


Figure 12. Behavioral performance scores on Berlin Gehoerbildung Scale (BGS). Error bars represent ± 1 standard errors (SE).

Preexisting differences in GM volume between aspiring professionals and amateur musicians

To characterize differences in grey matter volume between aspiring professionals and amateur musicians, we first computed a 2-sample t-test on the segmented whole-brain grey matter maps at measurement occasion B. This cross-sectional comparison yielded four significant clusters in superior parietal lobule, left superior temporal gyrus, right hippocampus, and right postcentral gyrus (see Table 5 and Figure 13), in which participants of the aspiring professional group showed greater grey matter volume than amateur musicians.

Table 5. Brain regions showing a significant group difference in grey matter volume between aspiring professionals and amateur musicians at measurement occasion B ($p < .005$, nonstationary smoothness corrected and cluster correction for expected voxels).

Area	*Peak coordinates (MNI)*	*T-score*	*Extent*
Right Hippocampus	22 -18 -24	3.54	567
Right superior parietal lobule	42 -38 52	4.00	415
Left superior/middle temporal gyrus	-52 -26 -9	3.63	348
Right postcentral gyrus	9 -34 74	3.54	111

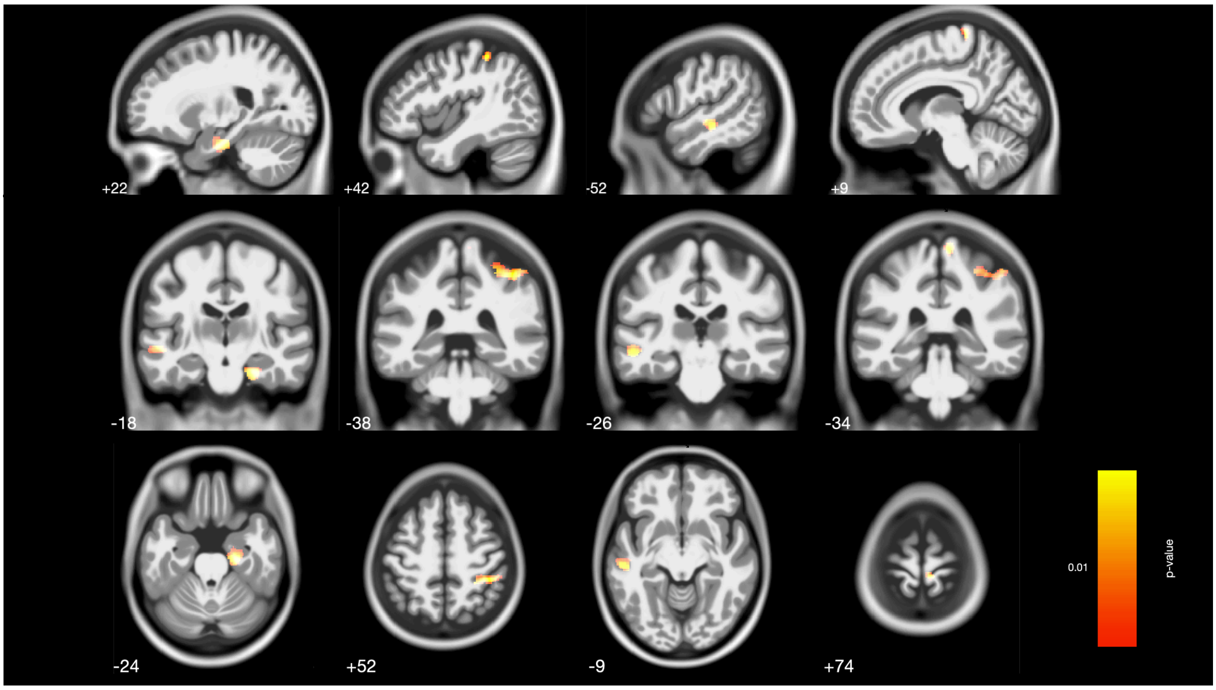
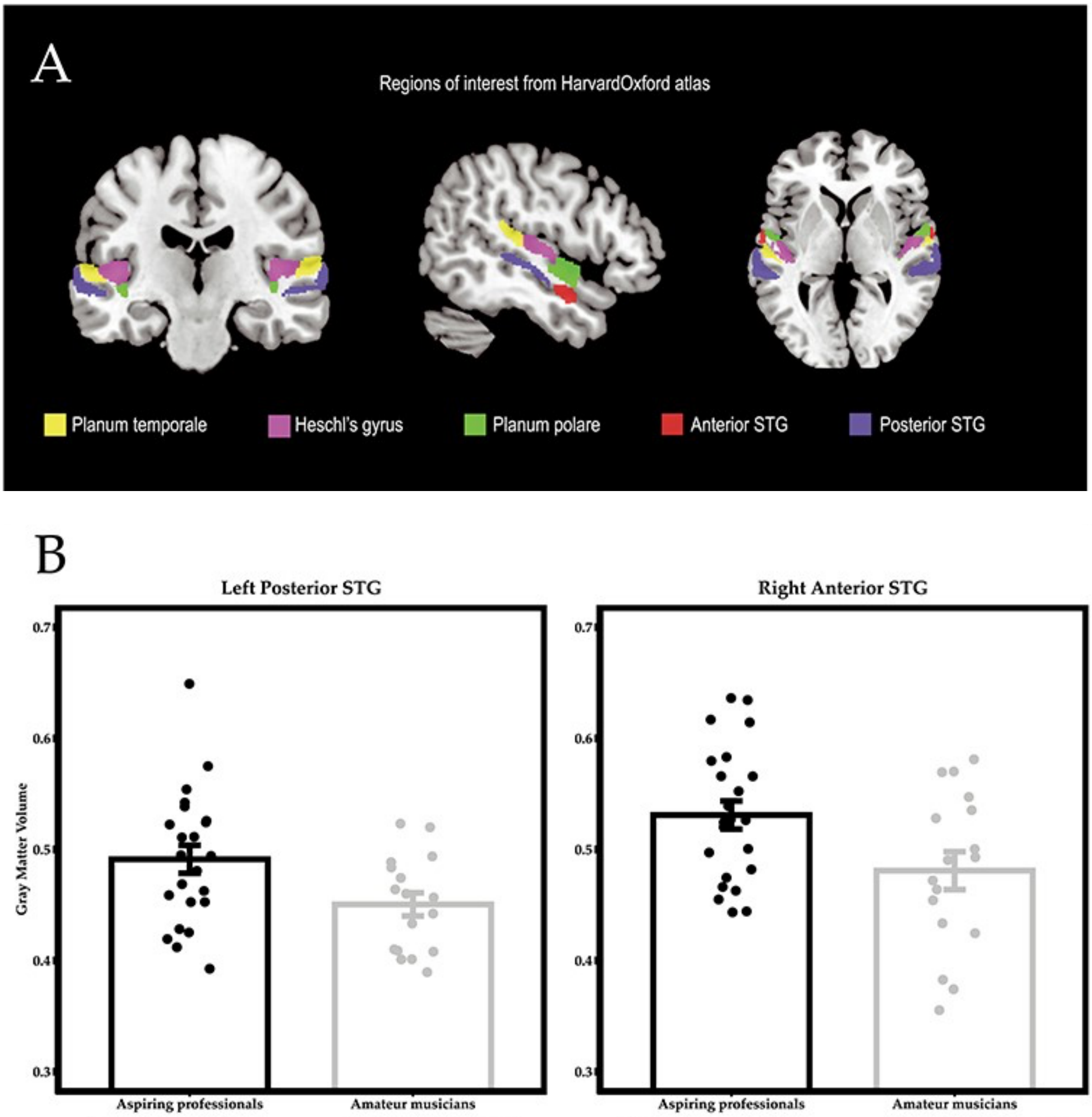


Figure 13. Regions of preexisting differences in grey matter volume between aspiring professionals and amateur musicians at measurement occasion B in hippocampus, superior parietal lobule, superior/middle temporal gyrus, and postcentral gyrus emerging in a whole-brain 2-sample t-test ($p < 0.005$, nonstationary smoothness corrected and cluster correction for expected voxels). Coordinates refer to MNI space. In all cases, volumes were greater in aspiring professionals than in amateur musicians.

An additional ROI analysis, focusing on primary and secondary auditory cortex further confirmed a significant difference in the right anterior portion of superior temporal gyrus (STG) ($t(38) = 2.40$, $p = .02$, *Hedges' g* = 0.7531) and the left posterior portion of STG ($t(38) = 2.37$, $p = .02$, *Hedges' g* = 0.7419) (see Figure 14). Analyses of grey matter volume differences in bilateral planum temporale, Heschl's gyrus, and planum polare showed the same tendency of greater grey matter volumes in aspiring professionals than in amateur musicians but failed to reach the threshold of statistical significance.



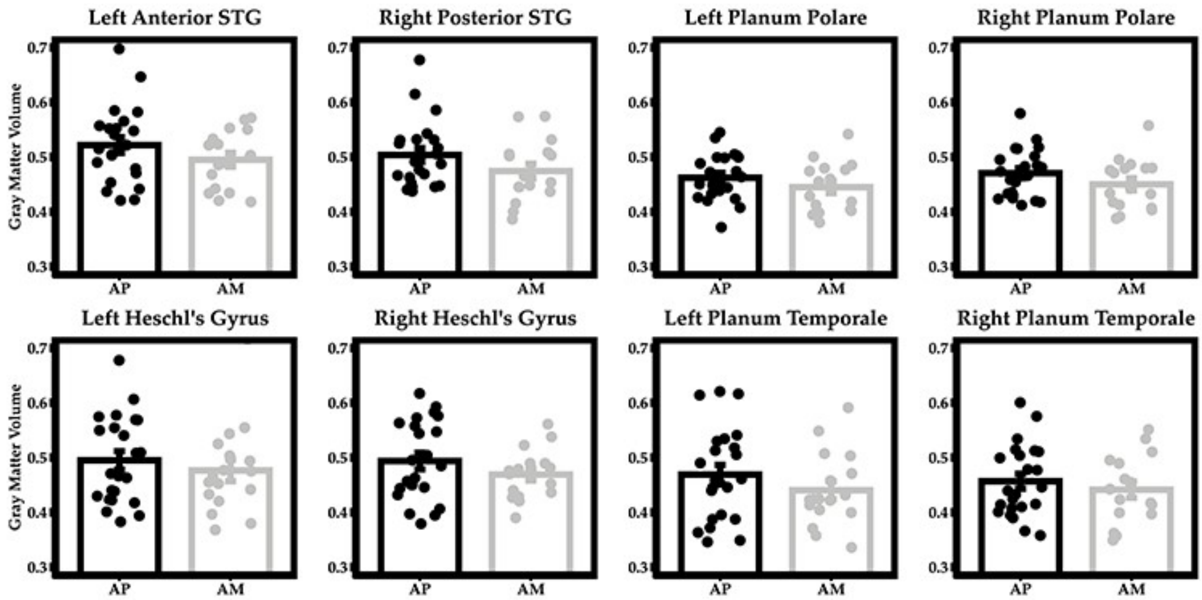


Figure 14. Region-of-interest (ROI) analyses showed a significant difference in grey matter volume in left posterior superior temporal gyrus (STG) and right anterior STG ($p < .05$). All other ROIs showed the same tendency of greater grey matter volumes in aspiring professionals than in amateur musicians but failed to reach the threshold of statistical significance.

Changes in GM volume over time

Given that the focus of this study was on differences in within-person changes between aspiring professionals and amateurs, we computed a whole-brain interaction on the segmented whole-brain grey matter maps. We found three significant clusters, namely in left planum polare, left posterior insula extending into planum polare, and left inferior frontal orbital gyrus extending into anterior insula (see Figure 15 and Table 6 for exact coordinates and *F*-scores). All of these clusters were driven by decreases in grey matter volume in aspiring professional musicians relative to amateur musicians (see Figure 15B).

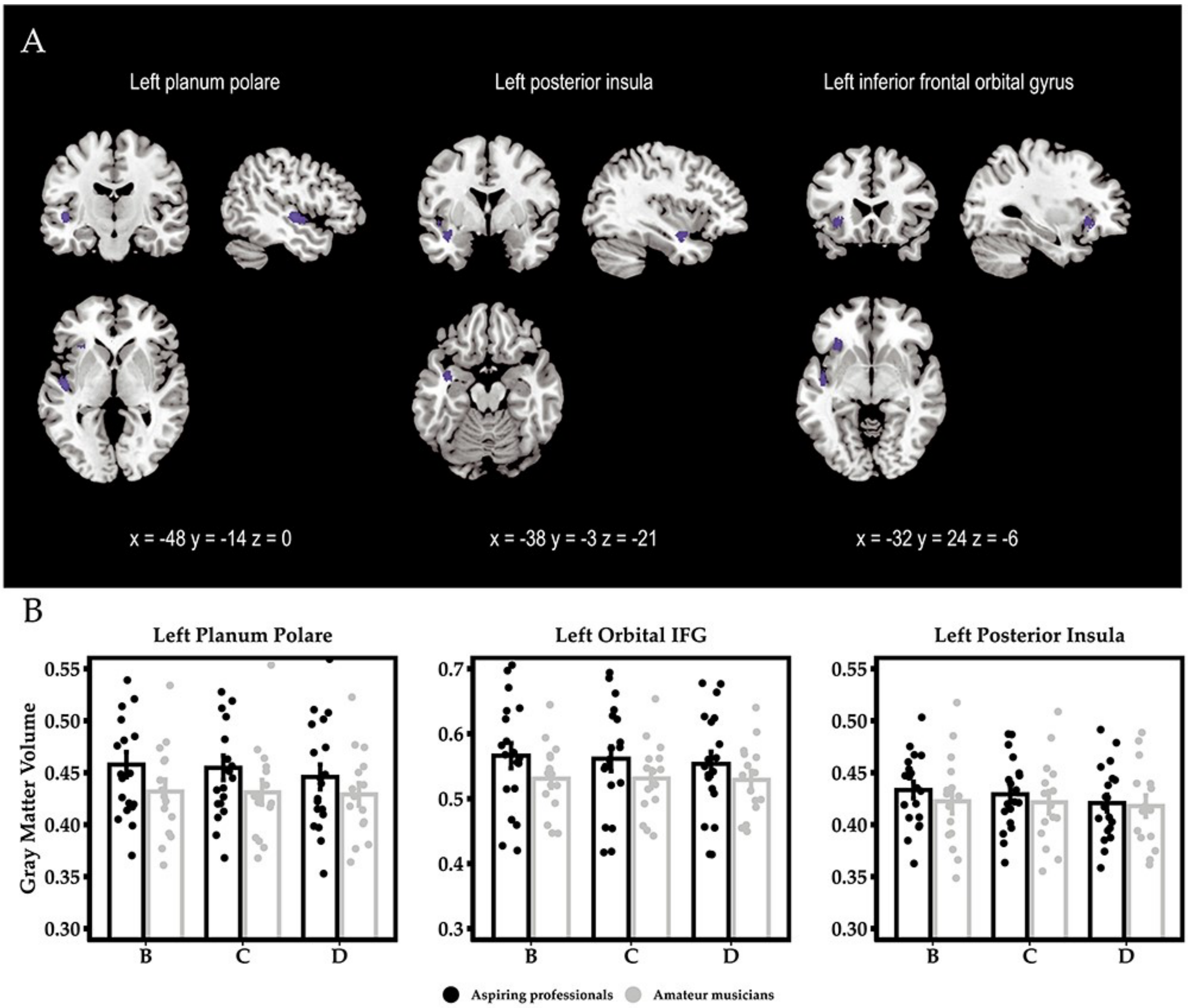


Figure 15. (A) Significant clusters in left planum polare, posterior insula and inferior frontal orbital gyrus emerging in a whole-brain time-by-group interaction analysis ($p < 0.001$, $k > 47$, corrected for nonstationary smoothness). Coordinates refer to MNI space. (B) Bargraphs with the extracted grey matter volume estimates of the significant clusters in the time-by-group interaction. This effect is driven by a decrease of grey matter volume in aspiring professionals compared to amateur musicians. Error bars represent ± 1 SE.

Table 6. Brain regions showing a significant interaction effect of Group (aspiring professionals vs. amateur musicians) and Time (timepoint B, C and D) in grey matter volume ($p < .001$, nonstationary smoothness corrected and cluster correction for expected voxels).

Area	*Peak coordinates (MNI)*	*F-score*	*Extent*
Left planum polare	-48 -14 0	23.02	292
Left posterior insula / planum polare	-38 -3 -21	18.40	181

Left inferior frontal orbital gyrus / anterior insula	-32 24 -6	16.06	181

For the left planum polare and inferior frontal orbital gyrus (IFoG), the observed decrements in estimates of grey matter volume in the group of aspiring professionals correlated with general music expertise as assessed by the BGS at measurement occasions B, C, and D (see Figure 16). A similar result was obtained at trend level for the posterior insula (left planum polare: $r_{\text{Time B}}(19) = -0.581^*$, $p = .009$; $r_{\text{Time C}}(19) = -0.517^*$, $p = .023$; $r_{\text{Time D}}(19) = -0.588^*$, $p = .008$; left posterior insula: $r_{\text{Time B}}(19) = -0.387$, $p = .102$; $r_{\text{Time C}}(19) = -0.525^*$, $p = .021$; $r_{\text{Time D}}(19) = -0.433$, $p = .064$; left IFoG: $r_{\text{Time B}}(19) = -0.558^*$, $p = .013$; $r_{\text{Time C}}(19) = -0.634^*$, $p = .004$; $r_{\text{Time D}}(19) = -0.589^*$, $p = .008$). This association was also true across the whole sample (left planum polare: $r_{\text{Time B}}(34) = -0.580^*$, $p < .001$; $r_{\text{Time C}}(34) = -0.523^*$, $p = .001$; $r_{\text{Time D}}(34) = -0.599^*$, $p < .001$; left posterior insula: $r_{\text{Time B}}(34) = -0.282$, $p = .106$; $r_{\text{Time C}}(34) = -0.398^*$, $p = .020$; $r_{\text{Time D}}(34) = -0.373^*$, $p = .030$; left IFoG: $r_{\text{Time B}}(34) = -0.586^*$, $p < .001$; $r_{\text{Time C}}(34) = -0.620^*$, $p < .001$; $r_{\text{Time D}}(34) = -0.620^*$, $p < .001$). Importantly, no such associations were found within the group of amateur musicians (all *p*s > .08).

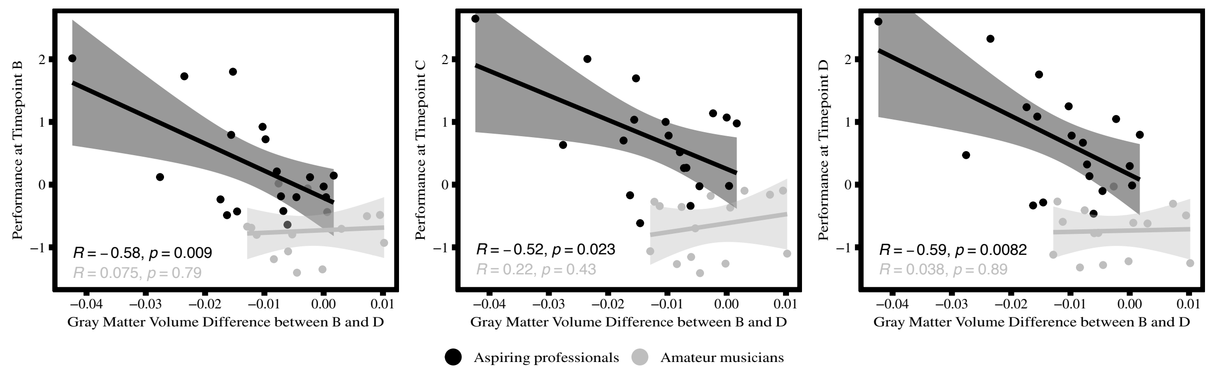


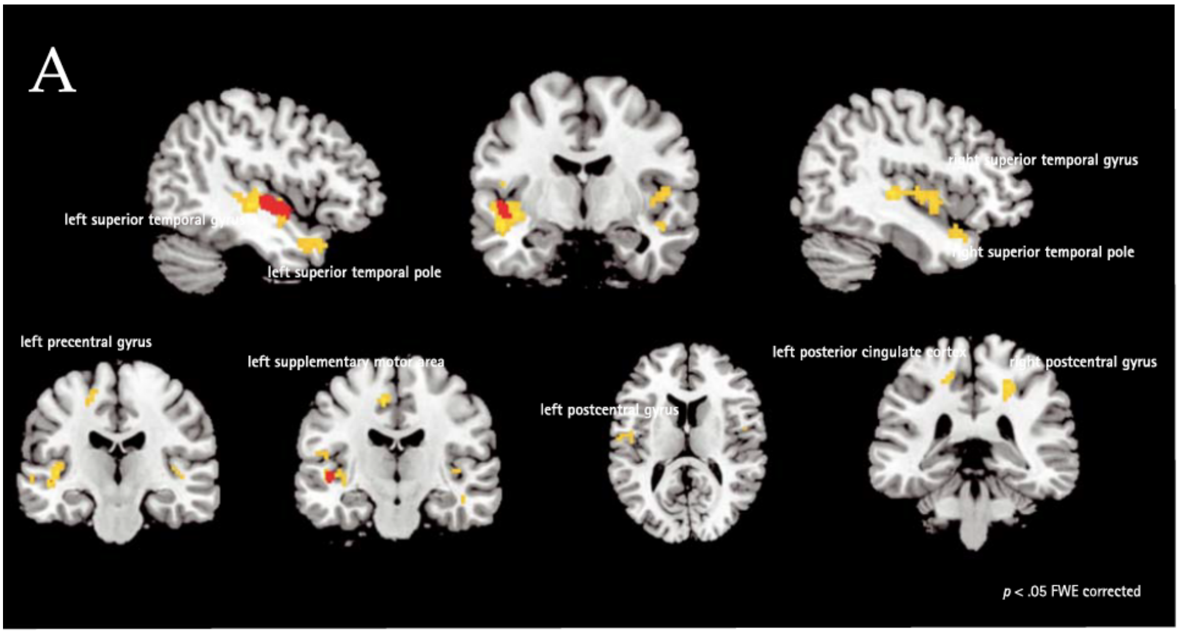
Figure 16. Correlations between decrease in gray-matter volume in left planum polare between timepoints B and D and behavioral performance in the BGS at measurement occasions B, C, and D, respectively.

Correlations in the total sample continued to differ reliably from zero in planum polare and inferior frontal gyrus after excluding one very high-performing individual who also exhibited the most pronounced structural decrease (but does not qualify as an outlier; left planum polare: $r_{\text{Time B}}(33) = -0.434^*$, $p = .012$; $r_{\text{Time C}}(33) = -0.354^*$, $p = .043$; $r_{\text{Time D}}(33) = -0.468^*$, $p = .006$; left IFoG: $r_{\text{Time B}}(33) = -0.519^*$, $p = .002$; $r_{\text{Time C}}(33) = -0.559^*$, $p = .001$; $r_{\text{Time D}}(33) = -0.561^*$, $p = .001$, but not in left posterior insula: $r_{\text{Time B}}(33) = 0.00$, $p = .999$; r_{Time}

$_C$ (33) = -0.162, p = .367; $r_{\text{Time D}}$ (33) = -0.141, p = .433). This means that those individuals showing the highest proficiency in this behavioral test were also the ones that exhibited the most pronounced decrease in grey matter volume. In contrast, the decrease in estimates of grey matter volumes did not correlate with improvements in music expertise ($r_{\text{planum polare}}$ (19) = -0.104, p = .671; $r_{\text{posterior insula}}$ (19) = -161, p = .483; r_{IFoG} (19) = -0.171, p = .483).

<u>Changes in functional connectivity</u>

To understand these changes in grey matter volume, we further investigated training-dependent changes in the coupling between brain regions. Here, we focused on the largest cluster of structural change located in left planum polare, that is, auditory cortex, and its correlations with other regions of the brain. We found increasing functional connectivity of the left planum polare to left and right auditory cortex, left precentral gyrus and left supplementary motor cortex, left posterior cingulate, and left and right postcentral gyrus over time in aspiring professionals compared to amateur musicians (FWE-corrected p-value of 0.05; see Figure 17).



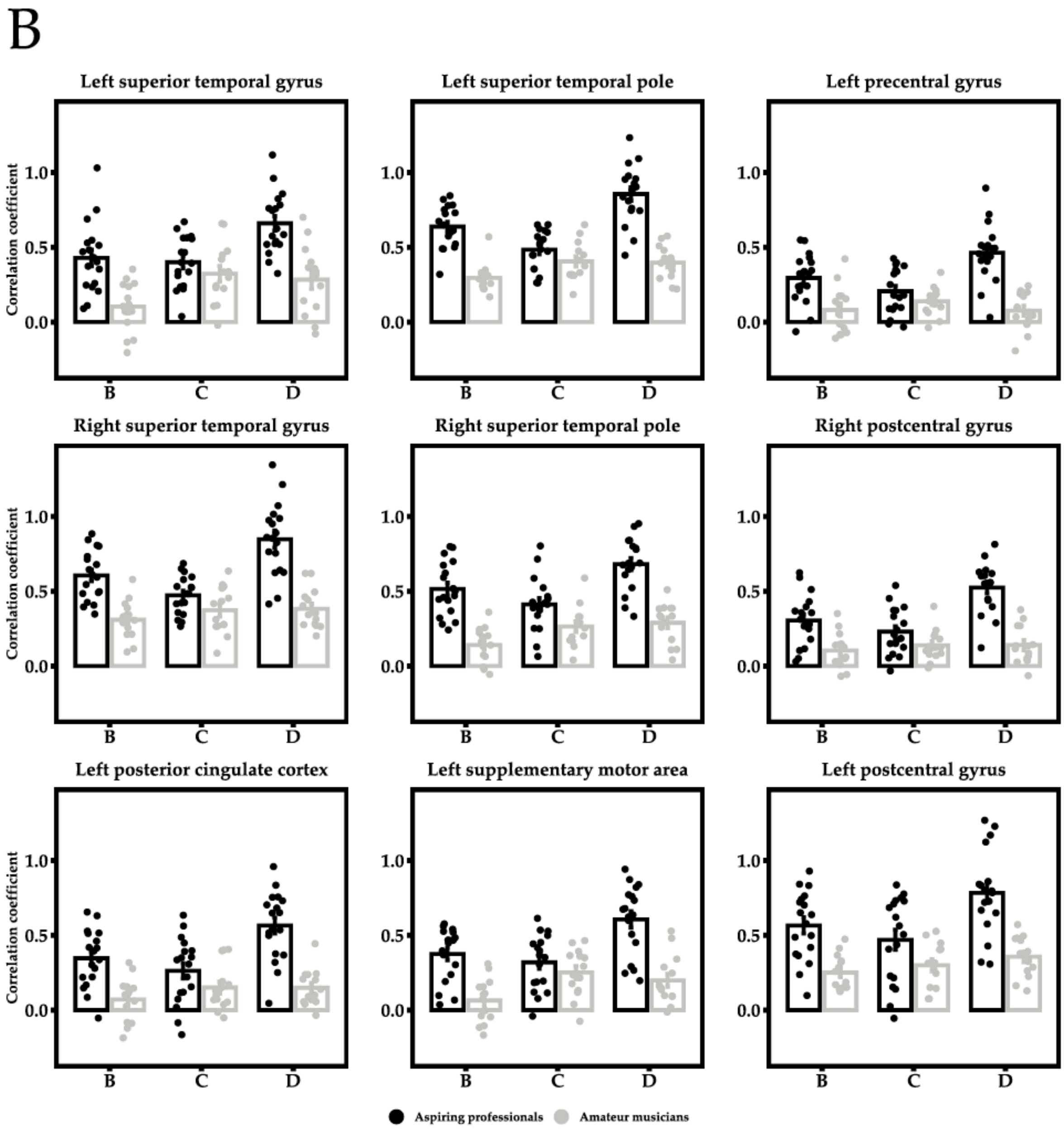


Figure 17. (A) Significant clusters exhibiting increased functional connectivity over time with left planum polare in aspiring professionals compared to amateur musicians (p < .05 FWE corrected). (B) Bargraphs with the extracted Fisher's z-transformed correlation coefficients from those significant clusters of the Time-by-Group interaction. Group-by-time interactions of the functional connectivity analysis were driven by increasing correlation coefficients in aspiring professionals relative to stable correlations among amateur musicians. Error bars represent ± 1 SE.

<u>Changes in graph-theoretical measures</u>

To further characterize changes in functional organization for the left planum polare and the whole brain, we conduced graph-theory analyses and compared network characteristics in the two groups over time. While there were no significant time-by-group interactions in any of the nodal measures for the left planum polare, there were significant time-by-group interactions for all global measures, namely for characteristic path length, global efficiency, local efficiency, and clustering (see Table 7 for exact numbers). In all of those measures, the group of amateur musicians showed no reliable mean change over time, whereas the group of aspiring professionals showed significant increases over time in all global metrics except for path length, which, as expected, decreased over time.

Table 7. Nodal and global measures of graph theoretical analyses at measurement occasions B, C and D, comparing aspiring professionals to amateur musicians. The nodal measures reported refer to the left planum polare.

Nodal Measures	**Aspiring professionals**			**Effect of time**		**Amateur musicians**			**Effect of time**		**Time-by-Group Interaction**	
	Time B	**Time C**	**Time D**	***F***	***p (FDR-corr.)***	**Time B**	**Time C**	**Time D**	***F***	***p (FDR-corr.)***	***F***	***p (FDR-corr.)***
Degree	98.83	101.1	107.3	8.04	0.011*	99.85	105.2	104.78	2.97	0.24	1.06	0.35
Path length	2.76	2.63	2.21	10.09	0.007*	3.10	2.48	2.53	1.65	0.24	23.06	0.08
Global efficiency	0.42	0.45	0.52	11.3	0.007*	0.37	0.46	0.45	1.51	0.24	3.55	0.08
Local efficiency	1.97	2.24	2.89	12.62	0.007*	1.54	2.28	2.13	2.88	0.24	4.09	0.08
Clustering	0.35	0.39	0.47	0.47	0.007*	0.29	0.39	0.37	3.18	0.24	2.88	0.08

Global Measures	**Aspiring professionals**			**Effect of time**		**Amateur musicians**			**Effect of time**		**Time-by-Group Interaction**	
	Time B	**Time C**	**Time D**	**F**	***p (FDR-corr.)***	**Time B**	**Time C**	**Time D**	**F**	***p (FDR-corr.)***	***F***	***p (FDR-corr.)***
Characteristic path length	2.89	2.78	2.36	11.15	0.004*	3.15	2.69	2.77	5.52	0.069	4.01	0.02*
Global efficiency	0.40	0.42	0.49	12.79	0.004*	0.36	0.43	0.41	4.57	0.069	5.17	0.02*

Local efficiency	1.84	2.03	2.65	12.39	0.004*	1.47	2.06	1.92	2.62	0.13	7.03	0.01*
Clustering	0.33	0.36	0.44	13.59	0.004*	0.28	0.36	0.35	5.06	0.069	4.002	0.02*

6.4 Discussion

In the present longitudinal study, we set out to investigate structural brain alterations and changes in functional connectivity in musicians intensely preparing for their entrance exam at a University of Arts. We found that grey matter volume decreased over time in comparison to amateur musicians in three clusters, namely left planum polare, posterior insula extending into planum polare, and left inferior frontal orbital gyrus extending into anterior insula. The biggest cluster of structural change was observed in left planum polare, which exhibited increased functional connectivity with left and right auditory cortex, left precentral gyrus, left supplementary motor cortex, left posterior cingulate cortex, and left and right postcentral gyrus. All of these regions have been previously identified to play important roles in music expertise (e.g., Luo et al. 2012; Groussard et al. 2014). The increase in connectivity for the region showing the greatest structural change was also reflected in results based on graph theory. Here, we observed changes over time in the global metrics, indicating participation of the planum polare in an increasingly complex network in the group of aspiring professionals compared to amateur musicians.

Our results once again speak to the malleability of adult brain structure to environmental influences (Kühn & Lindenberger, 2016; Lindenberger et al., 2017; Lövdén et al., 2013). The *left planum polare* as a region within the superior temporal gyrus, adjacent to left Heschl's gyrus, has been reported to show preferential activity to musical stimuli in comparison to other types of complex sounds, such as speech and non-linguistic vocalizations, and to integrate acoustic characteristics in the context of complex musical sounds, both in trained musicians and nonmusicians (Angulo-Perkins et al., 2014). In another study, left planum polare showed activity during high-level musical processing (Brown et al., 2004). In a study looking into functional networks underlying music processing and processing of vocalizations with a passive listening stimulation paradigm that included different vocal sound categories (i.e., song, hum and speech), left planum polare together with planum temporale and a group of regions on the right hemisphere that included the supplementary motor area, premotor cortex and the inferior frontal gyrus, showed stronger activations during music listening (Angulo-Perkins & Concha, 2019). Interestingly, left planum polare also showed activity during vocal musical listening, with and without lyrics, a finding pointing towards its role in music processing of temporally complex sounds, such as vocal music and speech. Overall, evidence suggests that the *planum polare* might be playing an intermediate role between the primary auditory cortex and other associative cortices, possibly extracting information (such as melodic patterns or pitch-interval ratios) required for further processing leading to perceptual evaluations (e.g., a same-different task), vocal production, and sensory-motor coordination to reproduce melodic or rhythmic sounds (Angulo-Perkins & Concha, 2019).

As an integration hub, the *insula* serves a plethora of different tasks, including sensory, emotional, motivational and cognitive functions (Gogolla, 2017). More specifically within the realm of music, the insula has often been discussed to reflect the emotional aspects of music processing (Blood & Zatorre, 2001; Koelsch, 2010; Koelsch et al., 2005) and is involved in autonomic regulation and sensory representation of emotion percepts (Koelsch, 2014). As aspiring professional musicians do not only have to perfect their technical skills but also have to hone their emotional sensitivity to music, it is conceivable that insula cortex, both anterior and posterior portions, evinces structural change.

Left inferior frontal gyrus is well known for its role in syntactic processing of language and music (Friederici, 2002; Nan & Friederici, 2012; Tillmann et al., 2006), as well as more broadly in general cognitive functions, such as top-down attention and working memory (Janata, Tillmann, et al., 2002; Schulze et al., 2011). Especially the orbitofrontal part has been associated with automatic appraisal and is activated by breaches of expectancy (Koelsch, 2014), a function crucial for aspiring professional musicians, as it helps them to discriminate, for instance, between expected and unexpected chord progressions. Interestingly, there have been findings of projections from the anterior superior temporal plane to the orbitofrontal cortex in rhesus monkeys (Petrides & Pandya, 1988), that go along well with a recent finding of functional connectivity of the left planum polare with orbitofrontal cortex in an fMRI study during music-evoked emotional processing (Koelsch et al., 2018).

Within all three of these regions, we have found structural decreases in the group of aspiring professionals, while volumes in amateur musicians remained stable. Importantly, we were comparing a group of individuals aspiring to become professional musicians to a group of amateur musicians who actually have a history of comparable years of playing an instrument but with different intensity and a different goal in mind. This stands in contrast to many other studies that have used nonmusicians as a comparison group. All of our participants look back on similar amounts of musical training, but the aspiring professionals presumably have been trying, for quite some time, to perfect their general ear-training skills in order to pass a highly competitive entrance exam. Accordingly, we found some structural differences between aspiring professionals and amateurs at the beginning of our observation period, with aspiring professionals exhibiting more grey matter volume in hippocampus, superior parietal lobule, superior/middle temporal gyrus, and postcentral gyrus. However, in the following weeks and months, aspiring professionals actually exhibited a decrease of grey matter volume over time compared to amateur musicians.

At first, the observed decrements in grey matter volume among aspiring professionals may seem counterintuitive. However, we have argued before that plasticity might in part be characterized by volume expansion followed by a selection process leading to a partial renormalization of overall volume (Wenger, Brozzoli, et al., 2017). In fact, given the large number of skills humans acquire during their lifetime, plasticity cannot be conceived as a process of perpetual growth (Changeux & Dehaene, 1989; Lindenberger et al., 2017; Wenger, Kühn, et al., 2017). According to the exploration–selection–refinement (ESR) model of human brain plasticity (Lindenberger & Lövdén, 2019; Lövdén et al., 2020) neuronal microcircuits potentially capable of implementing the computations needed for executing novel skills are, early in learning, widely probed, with a concomitant increase in grey matter volume. This phase of exploration is followed by phases of experience-dependent selection and refinement of reinforced microcircuits and the gradual elimination of novel structures associated with unselected circuits. It is tempting to speculate that the aspiring professionals had entered the selection and refinement phases of a plastic episode when they were recruited for participation in the present study. Clearly, this interpretation needs to remain tentative because we did not observe the full cycle of volume expansion followed by renormalization as in our previous study on motor training (Wenger, Kühn, et al., 2017) or as Quallo and colleagues did in their study on tool-use in monkeys (Quallo et al., 2009). Nevertheless, it offers a tenable explanation for the observed structural decreases in left planum polare, posterior insula, and inferior frontal orbital gyrus that needs to be corroborated in future work.

Thus far, data that are consistent with the ESR model have been primarily observed in early ontogeny or during motor skill acquisition; for review, see Lindenberger and Lövdén 2019. Acquiring a complex skill like playing an instrument, in combination with mastering the complexities of harmony and ear training is a different story. There are no data available yet that chart the sequential progression of plasticity over years of musical training. What is documented in the literature are, for the most part, cross-sectional studies showing differences in brain structure between musicians and nonmusicians. We can therefore only speculate how the alteration of brain structure in response to years of musical training that has evidently resulted in lasting volume expansion can be reconciled with an ESR view of plastic change.

One possibility is that changes occur as a sequence of *several* expansion–renormalization cycles that always conclude in only partial renormalization. This would in the long run result in a building-up of consistently "skill-optimized" grey matter structure. Obviously, we could not investigate this hypothesis in the current study. What we have observed is a decrease in estimates of grey matter volume in the group of musicians intensely preparing for an entrance exam, in comparison to a group of musicians still actively performing music on a daily basis but without intensive training. It is noteworthy that others have reported associations between smaller volume and higher expertise: In ballet dancers (Hänggi et al., 2010) and also in skilled pianists (Granert, Peller, Jabusch, et al., 2011), striatal volume was smaller in individuals with greater motor function efficiency. Furthermore, in a study investigating nonmusicians, amateurs, and expert musicians, there was a negative correlation between degrees of music expertise and grey matter density in right postcentral gyrus, bilateral precuneus/paracentral lobule, left inferior occipital gyrus, and bilateral striatal areas (James et al., 2014).

Following up on our structural results, we also investigated whether we would see indications of plasticity at the functional level. If what we observed here is indeed the second part of an expansion–renormalization cycle, then the left planum polare, which made up the largest patch of grey matter showing volume reduction, would be expected to undergo changes in functional connectivity. Hence, we expected that the planum polare would show increased connectivity throughout the brain, specifically to regions previously implicated in musical processing. Indeed, resting-state functional connectivity analyses revealed that over time, the left planum polare was better connected within left auditory cortex itself extending towards the superior temporal pole, and also to the right auditory cortex and superior temporal pole, left precentral and also supplementary motor area, left posterior cingulate cortex, and left and right postcentral gyrus, regions that have been shown before to matter in music expertise (Groussard et al., 2014; Luo et al., 2012).

Left auditory cortex has been shown to be involved in processing of melody (Bengtsson & Ullén, 2006) and more specifically also in musical semantic memory (Groussard et al., 2010). Left posterior cingulate cortex has been discussed in the context of integrating sensory information and emotional content, for example during reading musical notation (Hyde et al., 2009), in the context of familiarity tasks featuring well-known songs (Satoh et al., 2006), and in combination with autobiographical memories associated with musical excerpts (Ford et al., 2011). The supplementary motor area has been shown before to exhibit greater grey matter volume in musicians versus nonmusicians (Gaser & Schlaug, 2003) and has been implicated in the processing of sequential temporal structures (Bengtsson et al., 2009), pitch and timing repetition during both listening and performance tasks (Brown et al., 2013), as well as in rhythmic and melodic musical improvisation (de Manzano & Ullén, 2012).

Also, the results of our graph-theoretical analysis go along with our assumption of the malleability of adult brain function under the influence of training, leading to enhanced local and global communication among brain regions. This is reflected in all global measures of graph complexity we investigated, but not on the nodal level for the *left planum polare*.

At all measurement occasions, we observed significant correlations between individual differences in grey matter volume decrements and music expertise. In other words, the highest performing individuals exhibited the most pronounced decreases in grey matter volume in left planum polare, left insula, and left inferior frontal gyrus, thus, show the largest plastic change on the neural level. However, counter to expectations, we did not observe any significant correlations between changes in music expertise and changes in grey matter volume. One reason for the absence of such a change-change association is the high degree of stability of individual differences in music expertise over time. For instance, in aspiring professionals, we observed the following correlations in music expertise between adjacent measurement occasions (r_{AB} = .955; r_{BC} = .896; r_{CD} = .950; r_{DE} = .981).

We can only speculate about the neurobiological mechanisms that may have caused the observed reductions in grey matter volume. Synaptic changes including dendritic branching and axon sprouting as well as glial changes come to mind and we and others have elaborated on the exact potential mechanisms before (Lindenberger & Lövdén, 2019; Wenger, Brozzoli, et al., 2017; Zatorre et al., 2012). Future studies need to incorporate additional MR sequences specifically tailored to disentangle these processes, as for example T_1 maps (Lerch et al., 2017; Tardif et al., 2016).

The present study also has some further limitations that need be mentioned. First, there was no random assignment of participants to groups. Obviously, this caveat is inherent in the studied topic and is not easy to overcome. We have tried to limit this problem by recruiting two groups of participants with comparable years of playing an instrument. Still, there might be pre-existing differences between people who aspire to become professional musicians and people who consider themselves amateur musicians (Ullén et al., 2016). In addition, the stress to which aspiring professional musicians are exposed might have influenced the present results, as stress has been shown to result in grey matter volume reductions (Kassem et al., 2013). Thus, we cannot rule out that the observed decreases in grey matter volume might, to some extent, be related to stress, even though our findings of increased functional connectivity and the correlation with behavioral performance renders this explanation rather unlikely, and also auditory cortex does not belong to those regions typically affected by stress-related reductions (Lupien et al., 2009). Finally, the present samples were not systematically stratified by which main instrument the participants played. Hence, we may have missed out on effects that are specific to particular focal instruments, such as piano versus strings.

6.5 Conclusion

To conclude, we found that musicians intensely preparing for the entrance exam to a University of the Arts show reliable reductions in grey matter volume in regions pertinent to music expertise, whereas a group of amateurs not preparing for an exam did not show such changes. The planum polare, which was the largest grey matter cluster with volume reductions, showed increasing functional connectivity to other musically-relevant regions. This increase in connectivity was also reflected in global metrics of network integration and segregation based on graph theory. The present results are consistent with the ESR model of plastic change (Lindenberger & Lövdén, 2019; Lövdén et al., 2020), which posits an expansion of grey matter volume during early phases of skill acquisition, followed by partial renormalization (Wenger, Brozzoli, et al., 2017).

6.6 Supplementary material

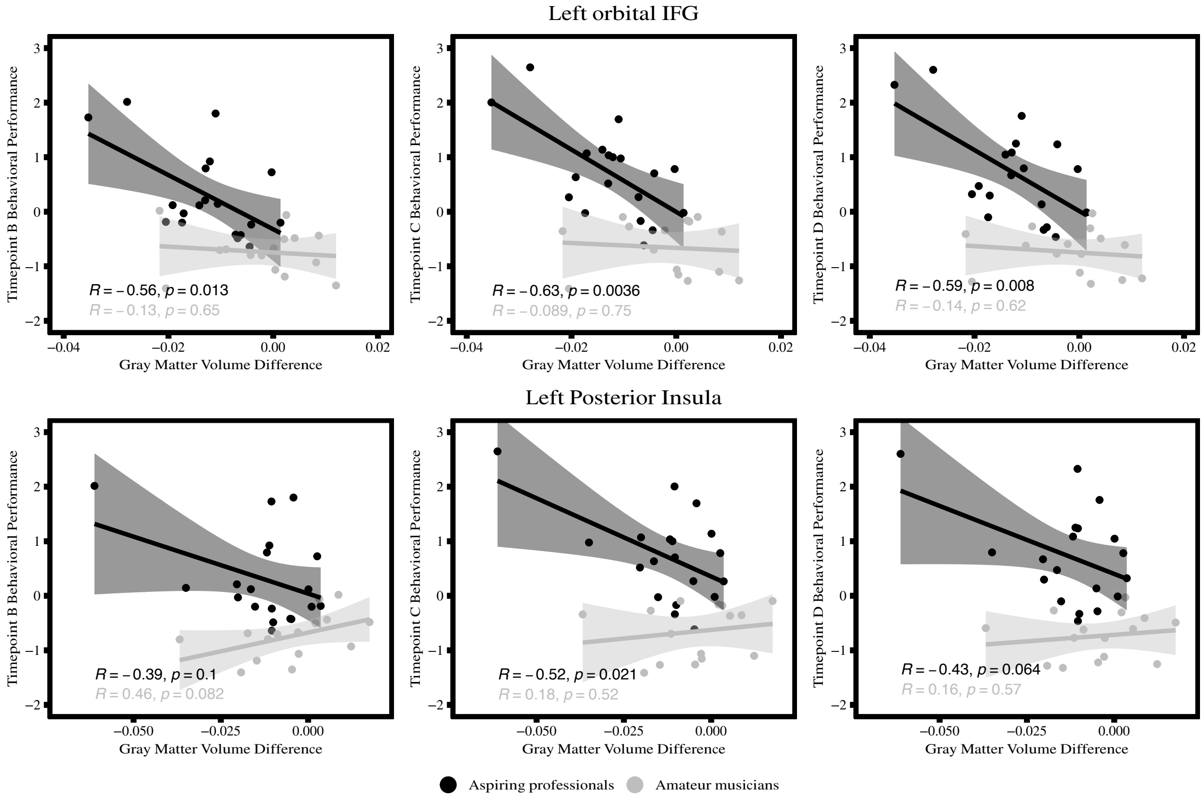


Figure 18. Correlations of grey matter volume changes from measurement occasion B to D in left orbital inferior frontal gyrus (IFG) and left posterior insula inferior frontal orbital gyrus with behavioral performance at measurement occasions B, C, and D.

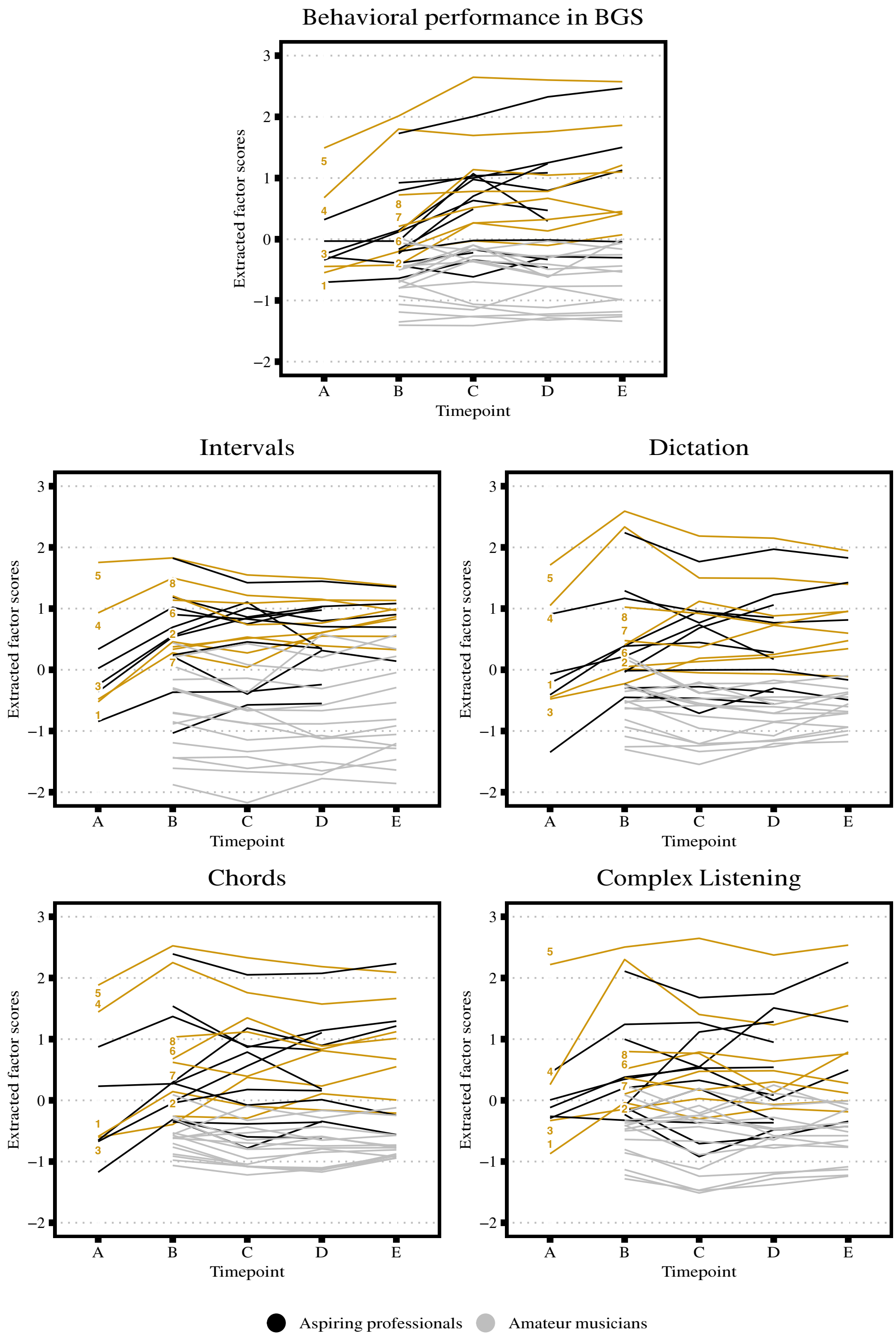


Figure 19. Line plots of individuals' time courses of the overall Berlin Gehoerbildung Scale (BGS) score representing music expertise, and the four factors representing sub-domains (Intervals, Dictation, Chords, and Complex Listening). Selected participants portrayed in Figure S2 (participants 1-8, all belonging to the group of aspiring professionals) are displayed in dark yellow lines here, to further illustrate their behavioral performance.

7 Discussion

This dissertation examined manifestations of functional brain plasticity both cross-sectionally and longitudinally in a group of individuals aspiring to become professional musicians and a group of amateur musicians, actively practicing music in their daily lives. Specifically, I sought to explore how the differing intensity of training and aspirations, setting apart these two groups, are reflected in functional brain organization, with a focus on functional connectivity and graph-theoretical measures. Furthermore, I investigated changes in functional organization of an auditory region, undergoing changes in grey matter volume, for the group of aspiring professional musicians, in the course of intensive musical training. The presentation of the projects follows a progressive widening of the scope of the processes under examination, beginning from effects of different levels of musical expertise on the performance of an interval recognition task, to a real-life experience of listening to music, and eventually extending to observations of changes over time in function, as training continues and intensifies.

The first project aimed to answer the question of whether functional connectivity among regions facilitating interval recognition differs in resting state between the two groups of different expertise levels. The rationale was that repetitious activity during practicing a particular aspect of musical training, like interval recognition, would be reflected in their functional organization in the absence of task performance. The second project addressed two questions, first, how different processing demands of two musical pieces are reflected in whole brain functional configurations, and second, how the two groups differ in their expression of these configurations and in the recruitment of brain regions, according to the demands posed by each musical piece. The third project evolved around the question of what kind of functional connectivity changes accompany changes in grey matter volume of a specific auditory region, found to decrease over time in volume for the group of aspiring professionals.

In the discussion section, I will first summarize the findings of each project and discuss their implications in relation to current literature. Then I will discuss some aspects pertaining to all three projects and extending overall to the field of experience-dependent plasticity research. Furthermore, I will address some challenges and limitations of the projects presented and finally, I will summarize the conclusions of this dissertation and briefly present suggestions for further exploration of the topics.

7.1.1 Expertise-related differences on resting state functional organization of a network facilitating intervals recognition

Interval perception and recognition is a crucial and foundational part of musical education and of everyday practice for musicians. It comes as no surprise that musicians outperform nonmusicians and novices in tasks assessing tonal processing, a finding often accompanied by enhanced activation in relevant brain regions (Bianchi et al., 2017; James et al., 2017; Schneider et al., 2002, 2005). These findings instigated the question of whether repetitive recruitment of regions facilitating interval recognition affects their connectivity in resting state. Furthermore, the functional organization of such a network of regions might differ between the group of aspiring professional musicians, undergoing intensive training, and the group of amateur musicians. For this purpose, I utilized an fMRI task where participants performed interval recognition, in order to localize brain regions facilitating the process. This task-relevant set of regions was further used to compute functional connectivity analysis and graph measures of average strength and global efficiency on resting state data acquired separately. These metrics were then correlated with behavioral performance in the fMRI task and in separately acquired behavioral measures of musical expertise. Aspiring professional musicians outperformed amateur musicians in all behavioral measures of interval recognition and exhibited greater network strength and global efficiency than amateur musicians. Both metrics correlated positively with performance in the fMRI task and the additional measure of interval identification ability.

Although the fMRI-task was not tailored exclusively to perception of intervallic relationships, an issue that will be discussed in the limitations' subsection (7.3), the brain regions detected by the localizer task have all been reported to take part in intervallic and tonal processing. Especially posterior parts of the STG bilaterally, extending to the planum polare and the right temporal pole are often reported in relation to processing of intervallic information, pitch processing, perceptual decision making and auditory working memory (Hyde et al., 2008; King et al., 2018; Nolden et al., 2013; Peretz & Zatorre, 2005; Zatorre & Belin, 2001). The left supramarginal gyrus is reported to facilitate short-term pitch memory and maintenance of pitch information (Schaal et al., 2015, 2017), while the putamen, alongside participation in many aspects of auditory processing, facilitates temporal and sequential aspects of tonal processing (Geiser et al., 2012; Kotz et al., 2009; Pando-Naude et al., 2021). Finally, the ventromedial prefrontal cortex is prominent in integrating sensory input and facilitating perception-based decision making, auditory working memory and maintenance of tonal information (Sharma & Bandyopadhyay, 2020; Plakke & Romanski, 2014; Janata et al., 2002).

Crucially, activation in those regions was common in both groups. Further analysis of group differences in the fMRI task showed that the group of aspiring professional musicians had additional activations in occipital regions, possibly indicating visualization of perceived intervals, as a strategy for interval identification.

The group differences in the graph metrics, with the aspiring professional musicians exhibiting higher average strength and global efficiency in this network of regions, suggest that superior performance on the side of aspiring professionals is facilitated by an overall more connected network of regions. This is further highlighted by the correlation of graph metrics with behavioral performance. However, the group differences in the graph measures cannot be directly compared with other findings in the literature. This is due to the fact that few studies have utilized graph measures in investigations of musical expertise. Furthermore, among those who have, there is wide variability in the choice of nodal or global measures and whether computation is based on task or resting state data, on whole brain parcellations or on specific subnetworks facilitating a process, like in this case. Nevertheless, findings from studies utilizing graph measures for investigating functional network organization in relation to expertise, converge on the fact that musicians exhibit increased connections in music-processing brain regions throughout the brain, as well as enhanced efficiency for both local and whole-brain information transmission (Loui et al., 2012; Alluri et al., 2017; Leippold et al., 2021; Paraskevopoulos et al., 2017). In line with these findings, the group differences in the graph metrics suggest that musical training affects brain networks organization.

A crucial aspect of the reported findings is that network organization of the regions facilitating task performance differs between the two groups in the absence of any task execution and correlates with behavior. Importantly, this was not the case for two other resting state networks that were used in a control analysis, the default mode network and the executive control network. This aspect brings in discourse the relationship of task fMRI with resting state fMRI and the relationship of resting state fMRI with behavioral performance under the scope of experience-dependent plasticity. Many studies have shown that task-related activation patterns can indeed be mapped onto resting state activations and resting state networks (Calhoun, Kiehl, & Pearlson, 2008; Cole et al., 2014; Cole et al., 2016; Di, Gohel, Kim, & Biswal, 2013; Simon-Vermot et al., 2018; Smith et al., 2009). In this perspective, resting state is often viewed as a baseline state, on which specific task demands act upon, further shaping and contributing to the activation patterns observed during task execution (Deco et al., 2013). In this sense, resting state functional connectivity may be considered indicative of the brain's functional repertoire, which explains findings of resting state functional connectivity predicting, or usually correlating with learning accuracy and behavioral performance in various domains. For example, resting state functional connectivity has been found to predict performance in face and scene recognition tasks (Collins et al., 2019) and in memory tasks (Ramot et al., 2019), and learning outcomes in visual perceptual learning (Baldassarre et al., 2012), in learning of an artificial tone system (Lumaca et al., 2019) and in learning foreign sounds (Ventura-Campos et al., 2013).

In relation to experience-dependent plasticity, resting state functional connectivity has proven valuable in uncovering changes in functional organization. Musicians exhibit strengthened connectivity in comparison to nonmusicians among regions of bilateral auditory cortices, premotor cortex, supramarginal and orbitofrontal regions (Fauvel et al., 2014; Luo et al., 2012; Palomar-García et al., 2017), as well as in thalamocortical networks (Tanaka et al., 2017). Differences in resting state functional connectivity, with use of both static and dynamic measures, have also been reported among brain regions across the entire brain, including also multisensory regions and regions of various cognitive functions, such as memory, language and attention (Hou et al., 2015; Hou & Chen, 2021; Luo et al., 2012). In these studies, focusing only on resting state, the differences are attributed to the effects of long and intensive musical training, with connections to specific processes being only speculative. In the case of this project, I aimed to narrow down such effects on the specific process of interval recognition. Importantly, the acquisition of the resting state data preceded any task execution, which could induce short-lasting modifications in resting state activations, as it is shown that resting state connectivity exhibits variability affected among others by preceding task activations (Guerra-Carrillo et al., 2014). Overall, the results suggest that the group of aspiring professional musicians spending more time in formal training not only exhibit superior behavioral performance, but also systematically recruits these regions together, resulting in strengthened connectivity among them in resting state.

7.1.2 Effects of processing demands and musical expertise on functional organization while listening to music

Listening to music is a complex experience and aspects associated with it, like enjoyment or appreciation, are shaped by a multitude of factors including familiarity, enculturation in specific music genres, or relevant training experience (Mencke et al., 2019). Studies examining correlates of musical expertise during unconstrained listening to music have shown that musicians, in comparison to nonmusicians, show greater activation in regions of auditory processing and higher integration among auditory, somatosensory and motor regions

(Angulo-Perkins et al., 2014; Bangert et al., 2006; Habermeyer et al., 2009; Oechslin et al., 2013). In the second project, I investigated both how processing demands of music pieces modulate brain states and whether groups of different musical expertise show differences in functional organization during listening to music. Participants were presented with two musical pieces, one piece by J.S. Bach, typically referred to as baroque music, and one piece by A. Webern, part of the movement of compositional innovations of the 20th/21st century and typically referred to as 2nd Viennese School. These two pieces differ in composition style and elicit different listening experiences. The piece of J.S. Bach belongs to a corpus of music familiar and enculturated for western listeners. This modulates predictive and expectancy processes evoking emotional states, reward and pleasure sensations (Koelsch et al., 2019; Mencke et al., 2019). Processing music by J.S. Bach probably shows higher similarity within the two groups, without excluding of course differences in processes which could arise when focusing on specific musical features. Music by A. Webern presents a challenging musical experience, for the inexperienced listener. It can be appreciated based on features that are not necessarily inherent to acoustic features, like previous exposure, context, expertise and personality traits, like openness to experience (Dean & Pearce, 2016; Omigie, Dellacherie, & Samson, 2017; Brattico, Brigitte Bogert, & Jacobsen, 2013; Nusbaum & Silvia, 2011; Reber, Schwarz, & Winkielman, 2004). This is mainly due to its compositional style; hierarchies and regularities, around which western musical tradition is based, are lacking as a reference point (Rosch, 1975), resulting in low information content (Dean & Pearce, 2016) and an experience of predictive uncertainty (Hansen & Pearce, 2014).

The different listening experiences elicited by these two musical pieces are indeed reflected in the overall brain states configurations. While listening to the piece by A. Webern, all participants spend overall more time in a state characterized by higher connectivity and lower modularity while this pattern reversed during listening to the piece by J.S. Bach. This finding is in line with findings from studies examining how processing demands modulate activation, connectivity and network configurations on cognitive tasks. Enhanced interregional connectivity and integration is considered an adaptive response in order to meet higher processing demands (Kitzbichler et al., 2011;Vatansever et al., 2015; Shine et al., 2016), while modularity appears to reflect local processing in tasks which are not particularly challenging or can be processed habitually (Cohen & D'Esposito, 2016; Shine & Poldrack, 2018). A tendency towards more modular organization has been shown in relation to motor training (Bassett et al., 2011, 2015) and remains an issue to be further explored in the auditory domain. To my knowledge, this is the first project to apply such a conceptual and methodological framework to musical processing demands.

The second question of this project evolved around whether the difference in musical expertise of the two groups affected their overall functional organization in relation to the processing demands posed by the musical pieces. Absence of group differences during listening to the piece by J.S. Bach in examination of graph theoretical measures based on static functional connectivity, is not surprising given the potential familiarity of both groups with this musical genre and tradition, in which they are probably highly enculturated. In line with this, familiarity with musical pieces is shown to elicit more similar responses among listeners (Madsen et al.,2019). Furthermore, musicians and amateur musicians have also been reported to show similar activation patterns particularly in musical processing tasks of lower difficulty (Oechslin et al., 2013). Of course, this does not exclude potential between-group differences in processing particular aspects like timbre, tonality or rhythm, which could be investigated separately by isolating such events of interest within the musical piece and looking at the activations they elicit, as done in other studies (Alluri et al., 2013; Saari et al., 2018; Toiviainen et al., 2014). On the contrary, during listening to the piece by A. Webern, the group of aspiring professional musicians showed an overall higher global efficiency, indicative of enhanced whole brain integration. Furthermore, the group of aspiring professional musicians exhibited higher degree, a measure of node centrality, and participation coefficient, a measure characterizing the contribution of regions in between-networks communication, in a multitude of regions, in comparison to the group of amateur musicians. A reverse pattern was not observed for any of those measures. These metrics offer a characterization of brain regions in terms of their role as hubs and their contribution in interregional communication within the whole brain network and the communities they belong to (van den Heuvel & Hulshoff Pol, 2010). In the condition of listening to the piece by A. Webern, aspiring professional musicians, in comparison to amateur musicians, exhibited higher degree in frontotemporal, occipital, parietal and striatal regions, all of which have been related to aspects of musical processing and have been shown to undergo structural and functional plastic changes in many studies (subsection 2.2). Furthermore, in the less demanding condition of listening to the piece by J.S. Bach, aspiring professional musicians only exhibited higher degree bilaterally in the caudate and higher participation coefficient in frontal and temporo-occipital regions. Within-group differences for the group of aspiring professionals while listening to the piece by A. Webern in comparison to listening to the piece by J.S. Bach, manifested in higher degree in temporal, frontal, parietal and occipital regions. Such within-group differences between the two listening conditions were not observed for amateur musicians. Interpretation of these findings is along the lines of literature suggesting that higher variability in between networks connectivity, here manifested in participation coefficient differences, is related to increased cognitive flexibility (Douw et al., 2016). Furthermore, flexible hub connectivity patterns, here evident particularly in the between listening conditions comparison for the aspiring professionals, are shown to facilitate adaptive novel task performance and to be modulated by task demands (Cole et al., 2013; Deco et al., 2011; Sadaghiani et al., 2015). These results suggest that aspiring professionals, due to their more extended and intense formal training, have a wider functional repertoire which they can utilize more flexibly in order to adapt to the processing demands.

7.1.3 Structural and functional brain plasticity in the course of musical training

The first two projects presented effects of musical expertise on functional organization cross-sectionally, in relation to interval recognition and unconstrained listening to music. In the third project, the focus shifted to longitudinal changes in functional connectivity for the group of aspiring professional musicians, as they follow intense preparatory courses for their entrance exams at Universities of Arts. VBM analysis applied on the structural MRI data of the first time point where both groups were fully recruited, identified pre-existing differences in grey matter volume between the two groups in the right hippocampus, the right superior parietal lobule, the left superior/middle temporal gyrus and the right postcentral gyrus. Structural VBM analysis on differential changes over time in the two groups identified the left planum polare, alongside the left posterior insula and the left inferior frontal orbital gyrus as regions undergoing decreases in grey matter volume over time, for the group of aspiring professionals. Particularly decreases in grey matter volume in the left planum polare correlated with improvements in performance in behavioral assessments of musical expertise. These findings motivated the investigation of changes over time in the connectivity profile of the left planum polare, a core region in auditory processing. For the group of aspiring professional musicians, functional connectivity of the left planum polare increased over time with parts of the left and right superior temporal gyrus, the left precentral gyrus, the left supplementary motor cortex, the left posterior cingulate cortex and the left and right postcentral gyrus. The increases in functional connectivity were complemented by increases over time in graph measures of local and global communication efficacy for the group of aspiring professional musicians.

The strengthening of functional connectivity among the left planum polare and the above-mentioned regions, parts of auditory and sensorimotor cortices, is in line with existing findings. All of the regions have been reported in relation to various aspects of musical processing, and are expected to be recruited together during execution and performance of musical activities, including ear training and instrument practicing (Criscuolo et al., 2022). In cross-sectional studies, increased functional connectivity among auditory and sensorimotor regions unilaterally and bilaterally is often reported (Fauvel et al., 2014; Hou et al., 2015; Leipold et al., 2021; Palomar-García et al., 2017; Zatorre et al., 2007) as well as with parts of the cingulate cortex, associated with control and attentional processes (Fauvel et al., 2014; Luo et al., 2014). Increases in functional connectivity among those regions have also been reported in longitudinal studies recruiting individuals without prior musical training. Drum training for eight weeks resulted in increased functional connectivity among superior temporal gyrus bilaterally (Amad et al., 2017), while keyboard training increased connectivity between auditory and motor regions (D'Ausilio et al., 2006; Lahav et al., 2007). In the longest longitudinal study of piano training so far, spanning 24 weeks, training was associated with increased functional connectivity between the right postcentral and the right precentral gyri, as well as between the auditory and the motor networks. Importantly, functional connectivity within the sensorimotor network and structural connectivity of the auditory-motor network were found to be positively correlated with practice time (Li et al., 2018, 2019). Although in the current study there was no collection of diffusion-weighted images, these results allow for speculation of potential changes in white matter microstructure of the corticospinal tract or the corpus callosum, connecting auditory with motor regions as well as contralateral regions in the two hemispheres, as has been reported in other studies (Bengtsson et al., 2005; Elmer et al., 2016; Imfeld et al., 2009; Leipold et al., 2021).

Particularly interesting in this project is that the changes in the connectivity profile of the left planum polare happen alongside decreases in its grey matter volume. In addition, decreases in grey matter volume are significantly correlated with improvements in performance in behavioral assessments of musical expertise. Co-examination of brain structure, function and behavior allows for a more comprehensive understanding of plasticity manifestations and interpretation of findings, especially those, like decreases in grey matter volume, which might at first glance appear counterintuitive. Interpretations of these findings regarding brain structure, function and behavior can be bridged within the exploration-selection-refinement model (Lindenberger & Lövdén, 2019). In this framework, decreases in grey matter volume are considered to capture a later stage of learning when renormalization of volume takes place, following previous expansion, facilitating learning at an earlier stage. Especially the left planum polare, a core region in a variety of auditory processes, might be highly probed during training, leading to expansion of neural circuitry in this area, and with learning progression and development of skillful processing, only a subset of formed relevant neural circuitry is further needed and sustained. This interpretation is supported by the improvements in behavioral performance and their correlation with the decreases in the volume of the left planum polare. Furthermore, the increases in its connectivity with other regions of sensory-motor and auditory processing, probably due to their repetitive recruitment during musical training, suggest enhanced functionality that facilitates performance of musical activities. Although there is evidence from visual and motor training studies that increases in functional connectivity might be transient effects that are followed by decreases in progression of training (Ma et al., 2011; Yotsumoto et al., 2008), connectivity among the regions reported here is a common finding in cross-sectional studies investigating correlates of musical expertise. Finally, it is rather intriguing that in cross-sectional studies, regions of the auditory cortex are usually reported to exhibit increases in grey matter volume (Bermudez & Zatorre, 2005; Gaser & Schlaug, 2003; Groussard et al., 2010; Palomar-García et al., 2017; Schneider et al., 2002, 2005) in contrast to the finding of this project. A possible explanation for that, given also the limited time scope of this study and the fact that those studies mentioned above recruit musicians who have completed their formal training, is that there might be multiple cycles of expansion followed by only partial renormalization.

7.2 Overall discussion

The three projects presented and discussed above address questions on plasticity manifestations in the brain's functional organization cross-sectionally and longitudinally. The whole study could be characterized as a hybrid of cross-sectional and longitudinal design. Participants are matched in their overall years of engaging with music, but already at the first time point of data acquisition they differ in their aspirations, commitment to training and hours spent on a daily basis for practicing and learning. This explains partly the between-group differences in aspects of music processing demonstrated in the first two projects, based on data acquired in the beginning of the study, at the first time point where both groups were fully recruited. At the same time, the study follows up within-group changes attributed to the intensive preparatory training of the aspiring professional musicians and in a sense glimpses into the processes that will lead to professional musical expertise for many of the participants of this group, as viewed in many studies referenced throughout this dissertation. The effects of training are investigated in the third project, where differences over time are reported for the aspiring professional musicians in measures of brain structure and function.

These projects and the study as a whole enrich discussions about long-lasting investigations of the factors contributing to expertise, the relationship of practice and ability and how these are depicted macroscopically on the neural level. As in many other neuroimaging studies, cited throughout this dissertation, the findings of the three projects here talk in favor of musical training effects in neuroanatomy and function of brain circuits. The magnitude of these effects is in many cases correlated with onset of training, years of practice and practice intensity (Bengtsson et al., 2005; Gaser & Schlaug, 2003; Sampaio-Baptista & Johansen-Berg, 2017; Steele et al., 2013), although not unequivocally (Abdul-Kareem et al., 2011; Han et al., 2009; Imfeld et al., 2009). Especially in relation to the onset of training, plastic changes evoked by early training, taking place alongside developmental and maturational brain changes, are considered to contribute to an individual's brain "metaplasticity", enabling faster and more stable skill acquisition in the future (Altenmüller & Furuya, 2016). However, onset of training, amount of practice, or years of training are not exhaustive predictors of expertise and musical ability. Genetic variability, heritability and gene-environment interactions are found to contribute to musical ability, either in relation to physical characteristics, or propensity to engage successfully in musical training (Mosing et al., 2014; Ullén et al., 2016). Furthermore, personality traits, general intelligence and motivation, affecting amongst others the quality of training, especially in relation to attention and commitment, also play important roles in the shaping of musical aptitude and expertise (Furuya, 2018). Crucially, the relation of these factors with training and ability is considered bidirectional, as for example training might develop and shape further pre-existing differences in general intelligence and working memory capacity (Ullén et al., 2016). From these factors, only pre-existing differences in grey matter volume and working memory were assessed, the latter with a numbers-updating task, which yielded no significant group differences. The other factors mentioned in this section, although not controlled for in the current study, are considered very important in interpreting the findings reported. Given the different aspirations of the two groups of the study, the differences in their motivation and intensity and presumably quality of practice are reasonably hypothesized. Speculatively, these factors might have affected training of the aspiring professional musicians already much earlier in time, following their decision to study at Universities of Arts.

A further point of discussion that the projects of this dissertation raise concerns the use of network neuroscience tools and specifically graph-theoretical measures in the study of experience-dependent plasticity. Extending the scope of functional plasticity manifestations beyond measures of activation strength and connectivity, the use of graph-theoretical measures allows for assessment of functional plasticity in terms of network organization and the role that brain regions play in efficient interregional interactions and communication. In the context of experience-dependent plasticity, measures like modularity and clustering, related to the brain's potential for adaptive responses (Meunier et al., 2010) and indicative of effortless or habitual performance of tasks (Cohen & D'Esposito, 2016; Shine & Poldrack, 2018), are indicating increasing proficiency in performance as it becomes more automatic and more dependent on local processing (Bassett et al., 2011, 2015). Global and local efficiency, as introduced in the projects above, are indicative of enhanced integration and local interregional communication for the group of aspiring professional musicians. In addition, flexibly switching between states of integration and segregation, an aspect shown to characterize superior performance in cognitive domains (Cole et al., 2013; Douw et al., 2016), might be suggestive of musical expertise in terms of efficiently utilizing the available functional repertoire based on demands, an aspect examined in the second project. Along the same lines, musical expertise appears to affect the hierarchical organization of regions acting as hubs and between subnetworks connectors under different conditions. Furthermore, use of graph-theoretical measures might contribute to testing hypotheses of conceptual frameworks, like the ESR model. For example, one of the predictions of the ESR model pertaining to reduced activations and interactions among training-specific and executive control regions with progression of training (Lindenberger & Lövdén, 2019; Lövdén et al., 2020), could be tested and should result in increases in modularity of subnetworks and decreases in between-networks communication for groups of higher expertise. Especially such metrics of modular organization and between-modules interactions might assist unravelling plasticity changes in domain-specific systems' organization, like the auditory and the motor system, and their interactions with cognitive control systems (Chein & Schneider, 2012). This can be particularly insightful for studies of musical training which is known to span multiple sensory, motor and cognitive subsystems.

7.3 Challenges and Limitations

In the following, I will first address limitations of each project separately and will then discuss some issues pertaining to all three projects.

In the first project, a network of regions facilitating interval recognition was examined with respect to between-group differences in average strength and global efficiency and with respect to its relation with behavioral performance. This network of regions was derived from analysis of an fMRI task, contrasting listening to intervals against pressing a button to respond. This contrast captures a variety of processes, including pitch perception, processing of the intervallic relationships of the sequentially presented tones, the harmonic processing of the simultaneously presented tones (chords), as well as the mental manipulation of the perceived intervals aided by working memory and presumably the comparison of the perceived intervals with pre-existing representations/templates of intervallic relationships in order to make a decision regarding the intervals perceived. Clearly, it is not exclusive to the processing of the intervallic relationships, and thus, throughout the dissertation, this network of regions is referred to as a network facilitating interval recognition. Further, some of the significant clusters of activation of this analysis are rather extensive, especially along the STG bilaterally, while the chosen spherical ROIs cover only a small part of these extended clusters, around the voxels where peak activation was noted. Thus, the ROIs, especially regarding the STG, are indicative of the locations of peak activation and not precise regarding the extent of activation. This chosen analysis approach was based on existing literature, with creation of ROIs around the coordinates of peak activation, regardless of cluster extent, being a standardized practice (Lumaca et al., 2019; Ramot et al., 2019; Ventura-Campos et al., 2013). Furthermore, the behavioral accuracy data of the fMRI interval recognition task were not normally distributed, which calls for cautious interpretation of the significant correlation between task accuracy with network strength and global efficiency. There is however a clear tendency of greater network strength associated with better performance not only in the fMRI interval recognition task, but also the “Intervals and Scales” measure of the Berlin Gehörbildung Scale (BGS), a behavioral measure of musical expertise administered outside of the scanner. In addition, given the small size of the network and the fact that it is fully connected, there is a lot of information shared between the graph measures, which are also highly correlated. Finally, the current results are not conclusive on whether amateur musicians fail to recognize some of the different intervals or were simply unable to correctly name them. Still, the correlation between network strength and global efficiency with behavioral performance suggests a link between the more general feature of music expertise, which includes learning to correctly identify intervals, and brain network measures.

In the second project, a first issue to address is that musical and acoustic features of the pieces are not time-locked to the neural signals captured by the fMRI. Descriptive analysis of the musical pieces highlights some of the differences in their tonal and rhythmic structures but specific occurrences of such features cannot be directly linked to the brain states. Furthermore, there is no information on participants' familiarity, exposure and aesthetic appreciation of the two musical pieces, aspects which would affect interpretation of the current results or would enable addressing further questions, regarding how familiarity, exposure and aesthetic appreciation shape participants processing of the pieces. It is shown that music preferences modulate functional connectivity between auditory regions and the hippocampus, as well as among regions of the default mode network, important for internally-focused thoughts (Wilkins et al., 2014). In relation to the methods applied, dynamic functional connectivity analysis requires some parameter choices, like window length or overlap of windows, which are shown to result in variable outcomes, as underlying processes of interest develop in different timescales (Lurie et al., 2019; Preti et al., 2017; Shine & Poldrack, 2018). Such issues were addressed by using parameters suggested in the literature to yield reproducible and robust results (Lurie et al., 2019; Preti et al., 2017; Shine & Poldrack, 2018). Furthermore, participation only in one state is allowed at a given time window, while multiple states might be present at a given point in time at varying degrees. The modularity index, computed here using maximization of the modularity function, partitions a network into a set of communities in a nondeterministic way and produces many near-optimal partitions of the network (Bassett & Gazzaniga, 2011; Sporns & Betzel, 2016). This issue is partly addressed by multiple iterations of the algorithm, followed by choosing the most stable partitions. The graph measure of degree, used here for hub detection, is only one of the available centrality measures and is thus not exhaustive in hub detection (van den Heuvel & Sporns, 2013). However, although use of different centrality metrics might yield slightly differentiated outcomes, the various centrality metrics are often found to be highly correlated (Zhao et al., 2019). Additionally, degree was computed on the whole brain network, and not within each region' community, as it is suggested by some studies (Power et al., 2013; van den Heuvel & Sporns, 2013), in order to compute within group comparisons for the group of aspiring professionals between the two listening conditions.

In the third project, a first point of consideration regards the decreases in grey matter volume reported. The group of aspiring professionals during this preparation period is possibly experiencing stress, a factor shown to be related with decreases in volume of brain regions (Kassem et al., 2013). However, the regions that are reported here, are not among those usually reported to be affected by stress (Lupien et al., 2009). Regarding the functional connectivity analysis, one may criticize that the seed for the functional connectivity analysis of the left planum polare was based on the parcellation of the Harvard-Oxford atlas (R.S. Desikan et al., 2006) and not on the significant cluster from the VBM analysis. This was done in order to enhance reproducibility and signal to noise ratio, which has been shown to be the case when using atlas-based parcellations (Faria et al., 2012). In addition, the planum polare is a small region, which minimizes the potential pitfall of averaging activity within a larger ROI and thus reducing sensitivity, a common concern when choosing regions from atlas-based parcellations.

Finally, there are some issues worth discussing which pertain to the study as a whole. A basic limitation is that participants were not randomly assigned to the different groups, an issue always arising in comparisons of groups with different levels of expertise. This limitation was attenuated, but not overcome, by matching participants of both groups on years of playing music. Participants in both groups already had years-long experience with music. The decisive difference between the groups lies in their intentions and professional aspirations regarding music. This is reflected in the intensity of daily practical and theoretical training that aspiring professionals undertake. Further, predispositions manifested as pre-existing differences in brain function and how they affect further learning are not taken into consideration (Zatorre, 2013). However, pre-existing differences in grey matter volume between the groups were examined and found to exist in the right hippocampus, the right superior parietal lobule, the left superior/middle temporal gyrus and the right postcentral gyrus. In the case of this study this would have been very challenging to account for, given that participants in both groups already have been learning music for years, in comparison to other longitudinal studies recruiting individuals without prior experience. In addition, there might be also pre-existing genetic differences and aspects of gene-environment interactions affecting individuals propensity to engage with musical training and to profit from it (Ullén et al., 2016).

The findings presented here regarding changes in functional organization in resting state could have been further enhanced by acquisition and analysis of diffusion-weighted data. The increased functional connectivity observed for the group of aspiring professionals in the first and third project, particularly among auditory and motor regions, could be underlined by changes in white matter tract connectivity and integrity in the pathways connecting these regions. This is a common finding in studies examining white matter microstructure in groups of different musical expertise (Bengtsson et al., 2005; Elmer et al., 2016; Imfeld et al., 2009; Leipold et al., 2021). Finally, both groups include keyboardists, string players, percussionists, wind instrument players and vocalists. There is evidence for differences among instrumentalists and singers in metrics of white matter (Halwani et al., 2011; Rüber et al., 2015), grey matter (Bangert et al., 2006; Rüber et al., 2015) and functional activations (Gebel et al., 2013), based on their primary instrument of practice. However, given the relatively small sample size of the study, participants were not stratified based on their instruments of focus and thus any instrument-specific effects on brain structure and function might have been missed.

7.4 Conclusions

The overall aim of the dissertation was to systematically investigate aspects of functional brain plasticity in relation to musical training and expertise. Crucial was the utilization of functional connectivity and tools from network neuroscience, given their potential to characterize plastic changes with a focus on interregional interactions and communication and changes in the organization of networks. Utilization of network neuroscience tools may be particularly insightful in relation to musical training, as it poses demands in multiple sensory, motor and higher order cognitive systems as well as in their interactions. In the first two projects, investigations of functional plasticity were carried out by cross-sectionally, at the first time point when both groups were fully recruited, addressing group differences on a specific aspect of music ability, namely interval recognition and on unconstrained listening to two musical pieces of different genres and compositional styles. In the third project, longitudinal changes in functional organization of a region undergoing changes in structure were investigated.

Resting state functional connectivity has already been shown to exhibit expertise-related differences between musicians and nonmusicians. Here, this is shown specifically within the context of interval recognition, relating behavioral performance with network connectivity and information transmission efficacy in a relevant brain network. In that sense, task-informed resting state fMRI is shown to capture persisting expertise-associated connectivity differences underlying task execution and relate them to expertise-associated behavioral performance. Aspiring professionals, presumably as a result of their training where ear training is of profound importance, seem to rely on a more connected and efficient auditory network that supports expert performance levels.

There is evidence that cognitive demands shape and modulate patterns of brain activity and connectivity, with higher demands probing brain configurations of greater interregional integration, while performance of trivial tasks or habitual processing is associated with configurations of increased modularity. Here, this is shown in relation to listening to music, specifically to two musical pieces, which evoke different listening experiences and probe different processing demands based on their compositional styles. Furthermore, the group of higher musical aptitude is shown to be primarily associated with increased connectivity in a multitude of brain regions, known for their relevance in various aspects of music processing, and higher global efficiency during processing demanding musical input. In addition, this group is shown to flexibly adapt recruitment of necessary neural circuitry based on the processing demands of each musical piece. Overall these findings underline the effect of musical expertise on network configurations in an ecologically valid setting.

Finally, musical training is shown to induce plastic changes assessed cross-sectionally and longitudinally. Here, it is shown that musicians intensely preparing for entrance exams to Universities of Arts underwent reduction in grey matter volume, in regions related to musical performance and expertise. This was not the case for amateur musicians actively practicing music in their daily lives. The left planum polare, which was the largest grey matter cluster of volume reduction, showed increasing functional connectivity to other regions relevant to music processing. Further, increased integration of regions in the whole brain was shown with graph measures, reporting both increases in global integration as well as in local interregional communication. These findings are interpreted within the framework of the ESR model of plastic changes (Lindenberger & Lövdén, 2019; Lövdén et al., 2020), which posits an expansion of grey matter volume during early phases of skill acquisition and learning, followed by partial renormalization (Wenger, Brozzoli, et al., 2017), while behavioral performance asymptotes or even further improves. Furthermore, the strengthening of functional connections among regions systematically recruited together speaks for the effects of training on shaping efficient neural circuity supporting enhanced performance.

7.5 Outlook & future directions

Considering how the work presented here could be extended and improved, I will first present some suggestions and additional research questions for each of the three projects and will then briefly present some research questions in relation to experience-dependent plasticity studies that I consider particularly interesting.

In relation to the first project presented, I would consider important to examine more closely the functional connectivity among the specific regions facilitating interval recognition during task execution. Specifically, using measures of effective connectivity and psychophysiological interactions, I would like to examine the inflow and outflow of information among these regions and which of them modulate information flow among the others. This way, group differences could also be assessed in relation to task execution, addressing the question of what aspects of connectivity within this network of regions facilitates superior performance for the aspiring professionals. Further, I would consider interesting to test the specificity of the reported network in relation to interval recognition, with a focus on the perception of intervals and in an effort to increase the specificity of the processes captured by the analysis of the task. For this purpose, I would consider introducing a slightly different fMRI task than the one reported here, in which an additional condition would be added where participants would listen to a pair of indeterminate pitch produced by unpitched percussion instruments. In this case, the two listening conditions would be contrasted with each other, instead of contrasting listening to the intervals with response, as is the case in the project presented here, which would increase specificity in relation to brain regions utilized in interval perception. An alternative to that would be an additional condition where participants would listen to the same intervals and make judgments regarding the timbre, a timbre identification task. A further alternative task design would be to introduce a same-different decision task where participants would have to decide which of two perceived intervals matches a target interval presented at the beginning of the trial. This would tap more on the perceptual side and be less relevant to recognition or identification aspects of processing, including labelling intervals which might be lacking in the group of amateur musicians.

Regarding the second project, a crucial improvement would be to additionally assess participants familiarity with the genres of the musical pieces presented and their aesthetic evaluation of them. There is evidence showing that the perceptual, cognitive and aesthetic experience of music is affected by multiple factors including enculturation, personality traits and musical training (Mencke et al., 2019). This way, further questions could be addressed, regarding how familiarity, exposure and aesthetic appreciation shape participants processing of the pieces. I would further like to extend the analysis targeting specific musical features, particularly in relation to violations of expectancies in tonality and rhythm, and look into participants functional responses in relation to such “events” within the musical pieces. This way, I would seek to address questions of whether participants with higher musical aptitude adapt their processing of musical features faster and more efficiently, after exposure with the complexity and ambiguity of contemporary music, aided by skillful listening in resolving perceived uncertainty.

In relation to the third project, I would like to address an additional question of how connectivity among whole resting state networks changes over time for the group of aspiring professional musicians. Specifically, I would like to investigate whether for the group of aspiring professional musicians connectivity among auditory and motor networks decreases over time with attentional and control networks, as there is evidence from the motor domain (Bassett et al., 2011, 2015), or is strengthened reflecting continuous recruitment of these networks together. Especially in relation to the regions found to decrease in volume over time, I would use temporal graph analysis to look into their community affiliations with progression of training. Given their different functional profiles, with the insula being a region of multimodal integration and the left planum polare being mostly implicated in auditory processing, it would be expected that they show differences over time in their participation in subnetworks.

Expanding on this last point, the functional profile of regions, whether they are multimodal and associative or unimodal and more domain specific, is worth investigating in relation to the plastic changes such regions exhibit in structure and function. A series of open questions call for further exploration. Are brain regions like regions of the sensorimotor system that are more connected within their subnetworks, specifically expected to show decreased activation and connectivity with other subnetworks, therefore being suggestive of efficient modular processing with progression of training? On the contrary, are then regions of multimodal associative cortices like the insula, serving multiple functions, expected to show enhanced connections with various domain specific systems, as a result of enhanced recruitment at some stages of learning? There is evidence that brain regions of sensorimotor cortices show more consistent connectivity profiles across individuals, while others show high variability (Mueller et al., 2013), especially within the multimodal association cortices, which, interestingly, have undergone marked evolutionary expansion (Mueller et al., 2013). Furthermore, how does the functional profile of brain regions relate to changes observed in grey matter? Are regions of domain specific systems more prone to undergo decreases in metrics of grey matter as a result of skill acquisition and more automatic processing relying on a highly efficient circuitry? For example, in relation to music training, regions reported to exhibit decreased values in metrics of grey matter are mainly part of the motor cortices and striatal regions (Granert, Peller, Gaser, et al., 2011; Hänggi et al., 2010; Haslinger et al., 2004; James et al., 2014; Vaquero et al., 2016), followed by regions in the auditory and visual system and the cerebellum, where less decreases have been observed (Baer et al., 2015; James et al., 2014; Vaquero et al., 2016). Is this suggestive of unimodal cortices, like the motor one and parts of the auditory system undergoing decreases due to increased processing automation, while other parts of the auditory system undergo increases in volume and thickness, reflecting expanded representations and storage of information? Given the multitude of underlying cellular mechanisms contributing to observed changes on the macroscale level, it is crucial to address such questions with advanced MRI techniques in experience-dependent plasticity research. These techniques provide quantitative maps of tissues' magnetic resonance properties which contribute to the MRI signal, allowing for more straightforward interpretations of the underlying biological mechanisms (Tardif et al., 2016) and the incorporation of such micro-structural parameters into connectomics (Larivière et al., 2019). The use of such acquisition techniques alongside utilization of tools from network neuroscience could advance understanding of experience-dependent plastic changes.

8 References

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9 List of Abbreviations

AFNI	analysis of functional neuroimages
ANOVA	analysis of variance
ANTs	advanced normalization tools
BGS	berlin gehörbildung scale
BIDS	brain imaging data structure
BOLD	blood oxygen level dependent
CSF	cerebrospinal fluid
DMN	default mode network
DVARS	delta variation signal
DWI	diffusion weighted imaging
EEG	electroencephalogram
EN	executive network
EPI	echo-planar imaging
ESR	exploration-selection-refinement model
FA	fractional anisotropy
FD	framewise displacement
FDR	false discovery rate
fMRI	functional magnetic resonance imaging
FWE	family-wise error
FWHM	full-width at half maximum
GLM	general linear modelling
GM	grey matter
IFG	inferior frontal gyrus
MD	mean diffusivity

MEG	magnetoencephalography
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
MTG	middle temporal gyrus
PFC	prefrontal cortex
ROI	region of interest
SE	standard error
SEM	structural equation modelling
SMG	supramarginal gyrus
STG	superior temporal gyrus
TMS	transcranial magnetic stimulation
VBM	voxel-based morphology
vmPFC	ventromedial prefrontal cortex
V1	primary visual cortex
WM	white matter

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Original Article

ORIGINAL ARTICLE

Observing Plasticity of the Auditory System: Volumetric Decreases Along with Increased Functional Connectivity in Aspiring Professional Musicians

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Abstract

Playing music relies on several sensory systems and the motor system, and poses strong demands on control processes, hence, offering an excellent model to study how experience can mold brain structure and function. Although most studies on neural correlates of music expertise rely on cross-sectional comparisons, here we compared within-person changes over time in aspiring professionals intensely preparing for an entrance exam at a University of the Arts to skilled amateur musicians not preparing for a music exam. In the group of aspiring professionals, we observed gray-matter volume decrements in left planum polare, posterior insula, and left inferior frontal orbital gyrus over a period of about 6 months that were absent among the amateur musicians. At the same time, the left planum polare, the largest cluster of structural change, showed increasing functional connectivity with left and right auditory cortex, left precentral gyrus, left supplementary motor cortex, left and right postcentral gyrus, and left cingulate cortex, all regions previously identified to relate to music expertise. In line with the expansion–renormalization pattern of brain plasticity (Wenger et al., 2017a. Expansion and renormalization of human brain structure during skill acquisition. Trends Cogn Sci. 21:930–939.), the aspiring professionals might have been in the selection and refinement period of plastic change.

Key words: gray matter changes, longitudinal, music expertise, structural brain plasticity, voxel-based morphometry

Introduction

Playing a musical instrument is an intense, multisensory experience. As music itself is a highly complex stimulus and musicians typically devote a lot of time to their training, they offer an excellent model for studying experience-dependent plastic changes in the brain. In our view, brain plasticity is an adaptive process that is triggered by a prolonged mismatch between the functional supply the brain structure can momentarily provide

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and the experienced demands the environment poses (Lövdén et al. 2010). In the last years, evidence for malleability of the adult brain structure to environmental challenges has been accumulating, mainly using magnetic resonance imaging (MRI; Lövdén et al. 2013). It has been shown repeatedly that brain volume and number of cells in animals differ depending on their living conditions, for instance, when comparing enriched versus standard rearing environments (Freund et al. 2013). In humans, various challenges such as learning how to juggle (Draganski et al. 2004), extensive studying (Draganski et al. 2006), becoming a taxidriver (Woollett and Maguire 2011), playing a video game (Kühn et al. 2014), or practicing tracing and writing with your nondominant hand (Wenger et al. 2017b) have been shown to elicit changes in estimates of gray-matter (GM) volume.

Music expertise has served as a particularly rich and fruitful domain for investigating plastic changes. It involves several sensory systems and the motor system, and it poses high demands on cognitive control processes (Münte et al. 2002; Jäncke 2009; Herholz and Zatorre 2012; Schlaug 2015). Most of the available data on the association between music expertise and the brain are cross-sectional rather than longitudinal. Musicians typically show an enlargement of brain areas associated with music-related processes in the auditory, motor, and visuospatial domain (Schneider et al. 2002; Gaser and Schlaug 2003; Hutchinson et al. 2003; Bermudez et al. 2009; James et al. 2014). Several brain areas, including the auditory cortices, the anterior corpus callosum, the primary hand motor area, and the cerebellum, differ in their structure and size between musicians and control subjects (Münte et al. 2002) and these volumetric differences have been shown to be of behavioral relevance (Schneider et al. 2002; Hyde et al. 2009; Foster and Zatorre 2010a). Groussard et al. (2014) have identified regions in the brain that increased in volume with the duration of practice, namely left hippocampus, right middle and superior frontal regions, right insula and supplementary motor area, left superior temporal, and posterior cingulate areas. Interestingly, while in some regions changes in volume seem to have occurred during early stages of musical training, like in left hippocampus and right middle and superior frontal areas, changes in other areas, specifically in left posterior cingulate cortex, superior temporal areas, and right supplementary motor area and insula, were more pronounced or even only occurred after several additional years of practice (Groussard et al. 2014). Similarly, James et al. 2014 have sorted music expertise into 3 levels to investigate its influence on GM density. Although they found GM increases with expertise in areas implicated in working memory and attentional control, that is in fusiform gyrus, mid orbital gyrus, inferior frontal gyrus, intraparietal sulcus, cerebellum, and Heschl's gyrus, they detected GM decreases with expertise in areas related to sensorimotor function, namely in perirolandic and striatal areas.

Arguably, musicians brains do not only differ structurally from nonmusicians but show also functional differences, such as strengthened functional coupling among relevant regions while performing musical tasks (Herholz and Zatorre 2012). Indeed, numerous functional imaging studies have compared musicians and nonmusicians and have observed differences in activity across many brain regions when individuals were performing musical tasks involving discrimination (Koelsch et al. 2005; Foster and Zatorre 2010b), working memory (Gaab et al. 2006), or production (Bangert et al. 2006; Kleber et al. 2010). Despite the many differences among the tasks used, one area that has been commonly activated in many of these studies was the left superior temporal gyrus (STG), a region that has been linked to musical training in terms of cumulative practice hours (Ellis et al. 2012). Of interest, functional MRI (fMRI) studies of perceptual learning with pitch tasks have resulted in both increases (Gaab et al. 2006) and decreases (Jäncke et al. 2001) of activity in auditory areas. Similarly, training to discriminate between melodies constructed of increasingly smaller intervals well below a semitone has been shown to be accompanied by general activation decrements in auditory regions, along with activation increases in frontal cortices (Zatorre et al. 2012a). Before training, the data had shown the expected dose–response function of more activity with increasing microtonal pitch interval size. After training, however, there was a reduction in blood oxygenation in response to increasing interval size (Zatorre et al. 2012a), suggesting that learning might decrease the number of neuronal units that are needed to perform the task (Poldrack 2000; Makino et al. 2016).

The brain exhibits spontaneous and systematic activity during wakeful rest (Biswal et al. 1995; van den Heuvel and Hulshoff Pol 2010; Zuo and Xing 2014). Exploiting this characteristic, one can compute resting-state functional connectivity that is based on spontaneous low-frequency fluctuations ($<$ 0.1 Hz) in the blood oxygen level-dependent signal (Biswal et al. 1995), and uncover functional networks that consist of brain regions frequently working together. Activity in the resting state may therefore reflect the repeated history of coactivation within or between brain regions for efficient task performance (Cole et al. 2012; Ventura-Campos et al. 2013; Baldassarre et al. 2016). Only a few studies have investigated differences in functional connectivity as a function of musical training. Pianists were found to show greater functional connectivity between left auditory cortex and the cerebellum than control participants (Luo et al. 2012). Regions with increases in GM in musicians compared with nonmusicians located in posterior and middle cingulate gyrus, left STG and inferior orbitofrontal gyrus have been shown to have increased connectivity to right prefrontal cortex, left temporal pole, left premotor cortex and supramraginal gyri (Fauvel et al. 2014). Palomar-García et al. (2017) tested for differences between musicians and nonmusicians in auditory, motor, and audiomotor connectivity and found stronger connectivity between right auditory cortex and right ventral premotor cortex, which correlated with years of practice. They also found reduced connectivity between motor areas that control both hands in those musicians whose instrument required bimanual coordination and increased volume in right auditory cortex. This increased GM volume correlated negatively with age at which training had begun and was related to increased connectivity between auditory and motor systems (Palomar-García et al. 2017).

As summarized above, most studies on neural correlates of music expertise rely on cross-sectional comparisons, rendering conclusions of whether observed group differences were preexisting or the result of learning de factor impossible. It has been impressively shown, though, that monozygotic twins, that is with identical genes, differing on musical training do indeed exhibit neuroanatomical differences, thereby providing strong support for the causal effects of training (de Manzano and Ullén 2018). Still, longitudinal studies with observations within the same individuals over time provide the most direct evidence for effects of musical training on neuroanatomy. We therefore used a variety of methodologies to characterize within-person changes over time in aspiring professionals intensely preparing for an entrance exam at a University of the Arts and compared these with skilled amateur musicians not preparing for a music exam. Specifically, we used anatomical MRI along with resting-state fMRI to investigate structural changes in GM volume that arise during this intense learning period within individuals over time and to analyze the changes in functional interactions that accompany these structural changes. We hypothesized that 1) in comparison to amateur musicians, aspiring professional musicians will show volumetric changes in regions previously identified to be relevant in the context of musical training, especially auditory cortex, 2) the regions of structural change will exhibit increased functional connectivity to other regions related to the auditory network, specifically, temporal regions, motor regions, and cingulate gyri, and 3) these changes in structure and functional connectivity will be related to behavioral performance.

Materials and Methods

Participants

We recruited a total of 24 young adults between 18 and 31 years [$M_{age} = 21.92$, standard deviation $\{SD\}_{age} = 3.72$] who were participating in preparatory courses offered at Berlin music schools to prepare them for an entrance exam at a University of Arts. These participants were either aspiring to study to become a conductor, composer, Tonmeister, or instrumentalist. As a control group, we recruited 17 amateur musicians between 18 and 27 years ($M_{age} = 23.12$, $SD_{age} = 3.43$) with at least 5 years of formal music education who were actively performing music in their daily lives but had no aspirations to perform music professionally. All participants had normal hearing, normal or corrected-to-normal vision, no history of psychological or neurological diseases, and no contraindication to participate in an MR study, such as metallic implants, tinnitus, or claustrophobia. The groups did not differ with respect to age ($t(39) < -1.05$, $P = 0.30$) or years of playing a primary instrument ($t(38) < 1$, $P = 0.68$ [Missing data for one participant]; aspiring professionals: $M_{years} = 12.04$, $SD_{years} = 4.57$; amateur musicians: $M_{years} = 12.74$, $SD_{years} = 5.97$).

Participants were paid up to 200€ for completion of the whole study (including up to 5 measurement time points with 1.5 h of MRI and 1.5 h of behavioral testing). The ethical board of the DGPs (Ethikkommission der Deutschen Gesellschaft für Psychologie) approved the study and written consent of all participants was obtained prior to investigation.

Experimental Design

Participants were invited for behavioral testing as well as MRI assessment between 1 and 5 times, depending on their availability, in the course of about a year, with approximately 10–12 weeks distance between appointments (see Fig. 1). Participants were put in the MR scanner for about an hour and 15 min and were then tested on the in-house developed "Berlin Gehoerbildung Scale" (BGS; Lin et al. 2021), a test to assess music aptitude at expert levels.

Behavioral Measure of Music Expertise

The BGS was designed by André Werner, a composer and collaborator in this study. It is a listening and transcription task focused on assessing music expertise (for a detailed description see Lin et al. 2021). It is informed by music theory and uses a variety of testing methods in the ear-training tradition. Items cover a variety of topics in music theory and ear training, including intervals, scales, dictation, rhythm, chords, cadences, identifying mistakes in music excerpts, and instrument recognition. Using behavioral data of amateur musicians, aspiring professional musicians, as well as 19 music students already studying music at a University of Arts, we have established a hierarchical structural equation model (SEM) of their behavioral performance the first time they encountered the test (Lin et al. 2021). The hierarchical model postulates 4 first-order factors of musical abilities, namely "Interval and Scales," "Dictation," "Chords and Cadences," and "Complex Listening," which together define a second-order factor of general music expertise. These 4 first-order factors load highly onto the second-order factor music expertise. We fixed the factor loadings of this established model and then extracted the second-order factor scores for each individual at each time point to investigate changes in performance over time. We then entered the factor scores into a repeated-measures analysis of variance with the factors Time (time point B, C, and D, as these measurement occasions provide us with the largest sample) and Group (aspiring professionals vs. amateurs).

MRI Data Acquisition

MR images were collected on a Siemens Tim Trio 3T MR scanner (Erlangen, Germany) with a standard 12-channel head coil. The MR measurement protocol included a T_1-weighted structural scan and a resting-state acquisition.

As structural images, we used a 3-dimensional (3D) T_1-weighted magnetization prepared gradient-echo sequence (MPRAGE) of 9.20 min with the following parameters: repetition time (TR) = 2500 ms, echo time (TE) = 4.77 ms, inversion time (TI) = 1100 ms, flip angle = 7°, bandwidth = 140 Hz/pixel, acquisition matrix = $256 \times 256 \times 192$, isometric voxel size = 1 mm^3. We used the prescan normalize option and a 3D distortion correction for nonlinear gradients.

Whole brain functional images were collected using a T_2*-weighted EPI sequence of 8 min sensitive to BOLD contrast (TR = 2000 ms, TE = 30 ms, FOV=$216 \times 216 \times 129$ mm^3, flip angle = 80°, slice thickness 3.0 mm, distance factor = 20%, voxel size = 3 mm^3, 36 axial slices, using GRAPPA acceleration factor 2). Slices were acquired in an interleaved fashion, aligned to genu splenium of the corpus callosum.

Structural Data Analysis

The structural MPRAGE images were processed by means of the Computational Anatomy Toolbox (CAT12; v1247; http://dbm.neuro.uni-jena.de/cat/) for SPM12 (v7219; www.fil.ac.uk/spm/) in Matlab 2017a (The Mathworks, Inc., Natick, MA, USA). Using default parameters, preprocessing of the data for voxel-based morphometry (VBM) involved intrasubject realignment, bias-field and noise removal, skull stripping, segmentation into GM and white matter (WM) and cerebrospinal fluid (CSF), and finally normalization to Montreal Neurological Institute (MNI) space using DARTEL to a 1.5 mm isotropic adult template provided by the CAT12 toolbox (whereby normalization is estimated for the mean image of all time points and then applied to all images). The resulting GM maps were smoothed with a standard Gaussian kernel of 8 mm full-width at half maximum (FWHM). These GM maps represent voxel-wise information on GM probability, which is an estimate of GM volume in an arbitrary unit (Ashburner and Friston 2005).

As for quality assurance, images were first visually inspected for artifacts prior to processing. Then, a statistical quality control based on intersubject homogeneity after segmentation was conducted using the "check homogeneity" function in CAT12. After preprocessing, all images were visually checked again for artifacts, whereby none were detected.

Statistical analysis of the GM maps was first carried out by means of a 2-sample t-test to test for initial structural differences between aspiring professional and amateur musicians at measurement occasion B (the first time point where both groups were

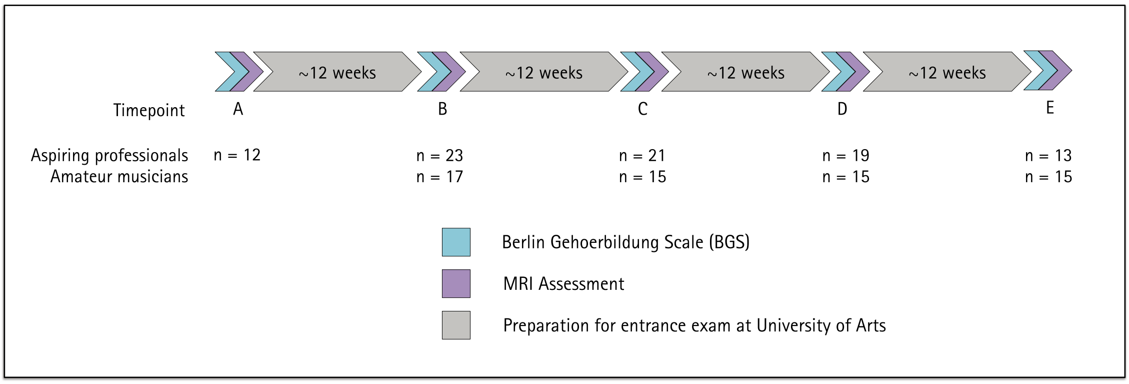

Figure 1. Overview of experimental design with recruitment numbers for aspiring professionals and amateur musicians at each time point.

fully recruited). This analysis included 23 aspiring professionals and 17 amateur musicians. An absolute GM probability threshold of 0.2 was applied. To control for type-I error, a significant effect was reported when the results met a peak-level threshold of $P < 0.005$ and when the cluster size exceeded the expected voxels per cluster threshold ($k > 259$ in this case) in combination with correction for nonisotropic smoothness. The expected voxels per cluster threshold was computed automatically by the CAT12 toolbox according to random field theory and empirically determines the minimum number of voxels that, in combination with a voxel-level threshold, clusters must meet in order to be reported (Hayasaka and Nichols 2004). In addition, correction for nonisotropic smoothness adjusts the minimum cluster size depending on the local smoothness of the data. This is a common cluster correction method used for whole-brain VBM analyses.

To further characterize pre-existing structural differences in GM volume between those two groups of musicians, we additionally performed a region-of-interest (ROI) analysis, focusing on left and right STG, as well as further divisions into bilateral planum temporale, Heschl's gyrus, and planum polare (taken from the HarvardOxford Atlas https://identifiers.org/neurovault.collection:262) (Desikan et al. 2006).

The main analysis in this paper focused on differential changes over time in the two groups of musicians by means of a whole-brain flexible factorial design with a focus on the interaction Time × Group. Since not all participants provided data for all time points, we based our statistical analysis on the middle 3 measurement occasions (B, C, and D) and only included those participants that contributed data to those 3 time points since this provided us with the highest possible number of participants for a longitudinal analysis in SPM. This resulted in a final sample of 19 aspiring professionals and 15 amateur musicians in this statistical comparison in which we tested for brain regions that display a significant increase or decrease in aspiring professionals compared with amateur musicians over time.

Again, an absolute GM probability threshold of 0.2 was applied. To control for type-I error, here, a significant effect was reported when the results met a peak-level threshold of $P < 0.001$ and when the cluster size exceeded the determined expected voxels per cluster threshold ($k > 47$) in combination with correction for nonisotropic smoothness (as explained above).

To investigate potential relationships between brain volume changes in the clusters showing a significant Time × Group interaction with behavioral performance, we extracted the data from significant clusters using the REX toolbox (ROI extraction tool; The Gabrieli Lab, MIT; http://www.alfnie.com/software), subtracted pretest from posttest values and correlated the difference scores with behavioral performance scores using Pearson's correlation coefficient.

Functional Data Analysis

Data preprocessing of the resting state data was performed using the toolbox DPABI (v4.0) (Yan et al. 2016) running under Matlab 2014b. The first 10 EPI volumes were discarded to allow the magnetization to approach a dynamic equilibrium. All volume slices were corrected for different acquisition times and then realigned. Individual structural images were coregistered to the mean functional image after realignment. The transformed structural images were then segmented into GM, WM, and CSF (Ashburner and Friston 2005). To remove head motion, respiratory and cardiac effects, we regressed out the Friston 24-parameter model (Friston et al. 1996) as well as signals from WM and CSF. In addition, linear and quadratic trends were also included as regressors since the BOLD signal exhibits low-frequency drifts. The DARTEL tool (Ashburner 2007) was used to normalize the functional data to the MNI template. We used a spatial filter of 4 mm FWHM and finally performed temporal filtering (0.01–0.1 Hz).

We then conducted an exploratory analysis by means of DPABI computing "functional connectivity maps with a seed region" consisting of left planum polare in MNI space, taken from the Harvard Oxford atlas (Desikan et al. 2006). To do so, the mean time course of all voxels in the seed region was used to calculate pairwise linear correlations (Pearson's correlation) with other voxels in the brain. Individuals' r values were normalized to z values using Fisher's z transformation.

Statistical analysis of the functional connectivity maps was again carried out by means of a whole brain flexible factorial design, again focusing on measurement occasions B, C, and D. We entered the images containing the z-transformed correlation values (between the seed region planum polare and all other voxels in the brain) in the second-level analysis with a focus on a time-by-group interaction, using a family-wise error (FWE) correction for multiple comparisons at $P < 0.05$ (cluster size $k = 20$ voxels). We used the REX toolbox to extract the z-transformed correlation coefficient values from within those clusters showing a significant time-by-group interaction.

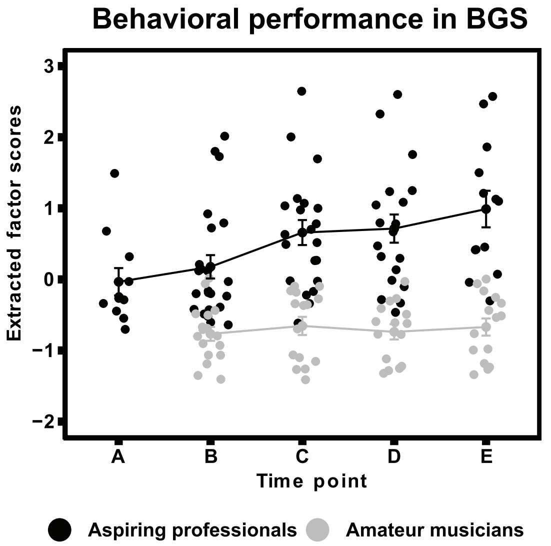

Figure 2. Behavioral performance scores on BGS. Error bars represent ±1 standard errors (SE).

Graph Theory Analysis

To perform connectivity analysis using graph-theory measures, we used BRain analysis using GraPH (BRAPH) theory (Mijalkov et al. 2017), a toolbox written in Matlab that uses the Brain Connectivity Toolbox codebase (https://sites.google.com/site/bctnet/) (Rubinov and Sporns 2010) to calculate network matrices. Such correlation matrices based on *r* correlation values were generated for every subject and then utilized in the calculation of both global and nodal measures. In this framework, nodes are brain regions based on the parcellation of the HarvardOxford Atlas (Desikan et al. 2006) and edges represent the correlations between the temporal activation of pairs of brain regions. The constructed matrix is a weighted undirected matrix, where the edges indicate the strength of the connection. As is common practice, only positive values were used in the calculation of nodal and global metrics (negative correlations were set to zero).

We computed 5 "nodal measures" including degree, path length, global efficiency, local efficiency, and the clustering coefficient. The "degree" refers to the total number of edges connected to a node. In the calculations, the weights of the connections were ignored by binarizing the connectivity matrix so that only edges with nonzero weights were considered connected. "Path length" refers to the average distance from a node to all others. The distance between two nodes is defined as the length of the shortest path between those nodes. In the case of a weighted undirected graph, the length of an edge is a function of its weight. Typically, the edge length is inversely proportional to the edge weight (i.e., a high weight implies a shorter connection). The "global efficiency" at the nodal level defines the efficiency of the information transfer from one region to the whole network, which assesses the average inverse shortest path length between one node and all other nodes in the network. The "local efficiency" as a nodal measure is calculated as the global efficiency of the node on the subgraph level, created by the node's neighbors. It reflects the efficiency of the information transfer from each region to the neighboring regions. The "clustering" coefficient at a nodal level is calculated as the fraction of triangles present around a node and is a measure of segregation.

Table 1. Brain regions showing a significant group difference in GM volume between aspiring professionals and amateur musicians at measurement occasion B ($P < 0.005$, nonstationary smoothness corrected and cluster correction for expected voxels)

Area	Peak coordinates (MNI)	T-score	Extent
Right hippocampus	22 −18 −24	3.54	567
Right superior parietal lobule	42 −38 52	4.00	415
Left superior/middle temporal gyrus	−52 −26 −9	3.63	348
Right postcentral gyrus	9 −34 74	3.54	111

It reflects the ability for specialized processing in small groups of nodes and is thus regarded a measure of local connectedness within a network.

In addition, we computed 4 "global measures," namely characteristic path length, global efficiency, local efficiency and clustering coefficient. The "characteristic path length" as a global measure is calculated as the average of the path lengths of all nodes. "Global efficiency" at the global level is the average of the global efficiency of all nodes in the graph and is inversely related to the characteristic path length. "Local efficiency" computed on the global level is the average of the local efficiencies of its nodes and reflects how well the nodes communicate with adjacent nodes. The "clustering coefficient" as a global metric is the average of the clustering coefficients of all nodes.

Statistical significance testing was done by extracting the values of the 3 measurement occasions for local and global measures for each subject from BRAPH and then testing for a time-by-group interaction separately for each nodal and global measure using SPSS, in the end applying a correction for multiple comparisons using the false discovery rate (FDR) algorithm (P value of 0.05; https://www.sdmproject.com/utilities/?show=FDR).

Results

Behavioral Results

Based on BGS results, aspiring professional musicians showed significantly higher levels of general music expertise than amateur musicians at measurement occasion B, which corresponds to an early phase of assessment, $t(32) = 4.57$, $P < 0.001$, Hedges' $g = 1.58$. Furthermore, aspiring professionals showed an increase in performance, whereas amateurs' performance remained relatively stable, as reflected by a significant time-by-group interaction, $F(2,64) = 8.53$, $P = 0.001$, partial η squared $= 0.21$ (see Fig. 2).

Preexisting Differences in GM Volume between Aspiring Professionals and Amateur Musicians

To characterize differences in GM volume between aspiring professionals and amateur musicians, we first computed a 2-sample *t*-test on the segmented whole-brain GM maps at measurement occasion B. This cross-sectional comparison yielded 4 significant clusters in superior parietal lobule, left STG, right hippocampus, and right postcentral gyrus (see Table 1 and Fig. 3), in which participants of the aspiring professional group showed greater GM volume than amateur musicians.

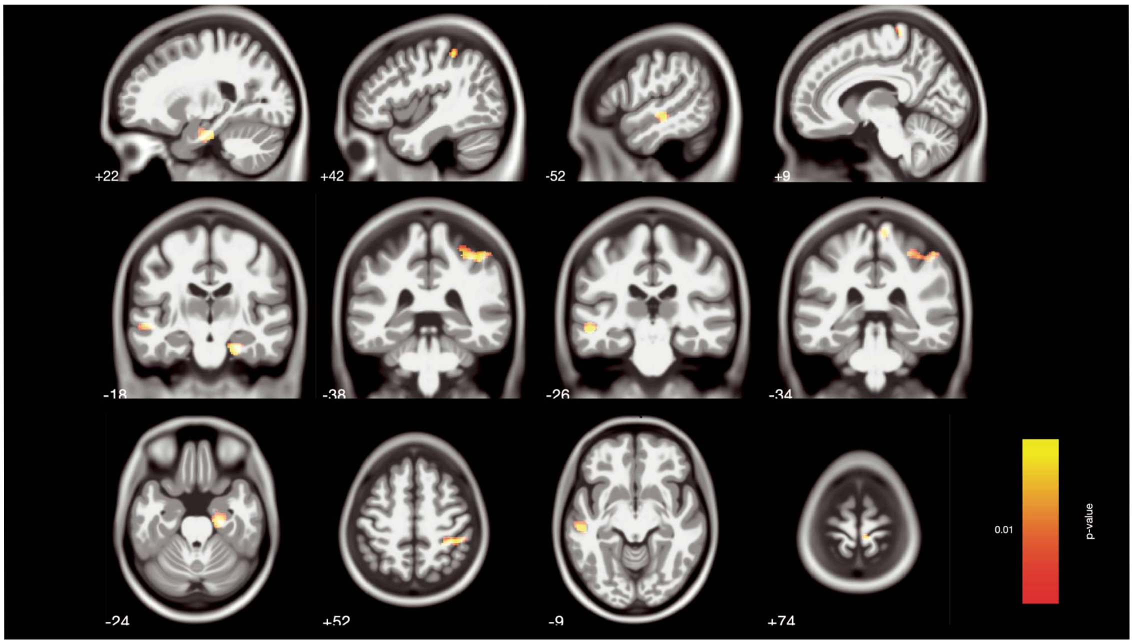

Figure 3. Regions of preexisting differences in GM volume between aspiring professionals and amateur musicians at measurement occasion B in hippocampus, superior parietal lobule, superior/middle temporal gyrus, and postcentral gyrus emerging in a whole-brain 2-sample *t*-test ($P < 0.005$, nonstationary smoothness corrected and cluster correction for expected voxels). Coordinates refer to MNI space. In all cases, volumes were greater in aspiring professionals than in amateur musicians.

An additional ROI analysis, focusing on primary and secondary auditory cortex further confirmed a significant difference in the right anterior portion of STG ($t(38) = 2.40$, $P = 0.02$, *Hedges' g* $= 0.7531$) and the left posterior portion of STG ($t(38) = 2.37$, $P = 0.02$, *Hedges' g* $= 0.7419$) (see Fig. 4). Analyses of GM volume differences in bilateral planum temporale, Heschl's gyrus, and planum polare showed the same tendency of greater GM volumes in aspiring professionals than in amateur musicians but failed to reach the threshold of statistical significance.

Table 2. Brain regions showing a significant interaction effect of Group (aspiring professionals vs. amateur musicians) and Time (time point B, C, and D) in GM volume ($P < 0.001$, nonstationary smoothness corrected and cluster correction for expected voxels)

Area	Peak coordinates (MNI)	F-score	Extent
Left planum polare	−48 −14 0	23.02	292
Left posterior insula/planum polare	−38 −3 −21	18.40	181
Left IFoG/anterior insula	−32 24 −6	16.06	181

Changes in GM Volume over Time

Given that the focus of this study was on differences in within-person changes between aspiring professionals and amateurs, we computed a whole-brain interaction on the segmented whole-brain GM maps. We found 3 significant clusters, namely in left planum polare, left posterior insula extending into planum polare, and left inferior frontal orbital gyrus (IFoG) extending into anterior insula (see Fig. 5 and Table 2 for exact coordinates and *F*-scores). All of these clusters were driven by decreases in GM volume in aspiring professional musicians relative to amateur musicians (see Fig. 5B).

For the left planum polare and IFoG, the observed decrements in estimates of GM volume in the group of aspiring professionals correlated with general music expertise as assessed by the BGS at measurement occasions B, C, and D (see Fig. 6). A similar result was obtained at trend level for the posterior insula (left planum polare: $r_{\text{Time B}}$ $(19) = -0.581^*$, $P = 0.009$; $r_{\text{Time C}}$ $(19) = -0.517^*$, $P = 0.023$; $r_{\text{Time D}}$ $(19) = -0.588^*$, $P = 0.008$; left posterior insula: $r_{\text{Time B}}$ $(19) = -0.387$, $P = 0.102$; $r_{\text{Time C}}$ $(19) = -0.525^*$, $P = 0.021$; $r_{\text{Time D}}$ $(19) = -0.433$, $P = 0.064$; left IFoG: $r_{\text{Time B}}$ $(19) = -0.558^*$, $P = 0.013$; $r_{\text{Time C}}$ $(19) = -0.634^*$, $P = 0.004$; $r_{\text{Time D}}$ $(19) = -0.589^*$, $P = 0.008$). This association was also true across the whole sample (left planum polare: $r_{\text{Time B}}$ $(34) = -0.580^*$, $P < 0.001$; $r_{\text{Time C}}$ $(34) = -0.523^*$, $P = 0.001$; $r_{\text{Time D}}$ $(34) = -0.599^*$, $P < 0.001$; left posterior insula: $r_{\text{Time B}}$ $(34) = -0.282$, $P = 0.106$; $r_{\text{Time C}}$ $(34) = -0.398^*$, $P = 0.020$; $r_{\text{Time D}}$ $(34) = -0.373^*$, $P = 0.030$; left IFoG: $r_{\text{Time B}}$ $(34) = -0.586^*$, $P < 0.001$; $r_{\text{Time C}}$ $(34) = -0.620^*$, $P < 0.001$; $r_{\text{Time D}}$ $(34) = -0.620^*$, $P < 0.001$). Importantly, no such associations were found within the group of amateur musicians (all $Ps > 0.08$).

Correlations in the total sample continued to differ reliably from zero in planum polare and inferior frontal gyrus after excluding one very high-performing individual who also exhibited the most pronounced structural decrease (but does not qualify as an outlier; left planum polare: $r_{\text{Time B}}$ $(33) = -0.434^*$, $P = 0.012$; $r_{\text{Time C}}$ $(33) = -0.354^*$, $P = 0.043$; $r_{\text{Time D}}$ $(33) = -0.468^*$, $P = 0.006$; left IFoG: $r_{\text{Time B}}$ $(33) = -0.519^*$, $P = 0.002$; $r_{\text{Time C}}$ $(33) = -0.559^*$, $P = 0.001$; $r_{\text{Time D}}$ $(33) = -0.561^*$, $P = 0.001$, but not in left posterior insula: $r_{\text{Time B}}$ $(33) = 0.00$, $P = 0.999$; $r_{\text{Time C}}$ $(33) = -0.162$, $P = 0.367$; $r_{\text{Time D}}$ $(33) = -0.141$, $P = 0.433$). This

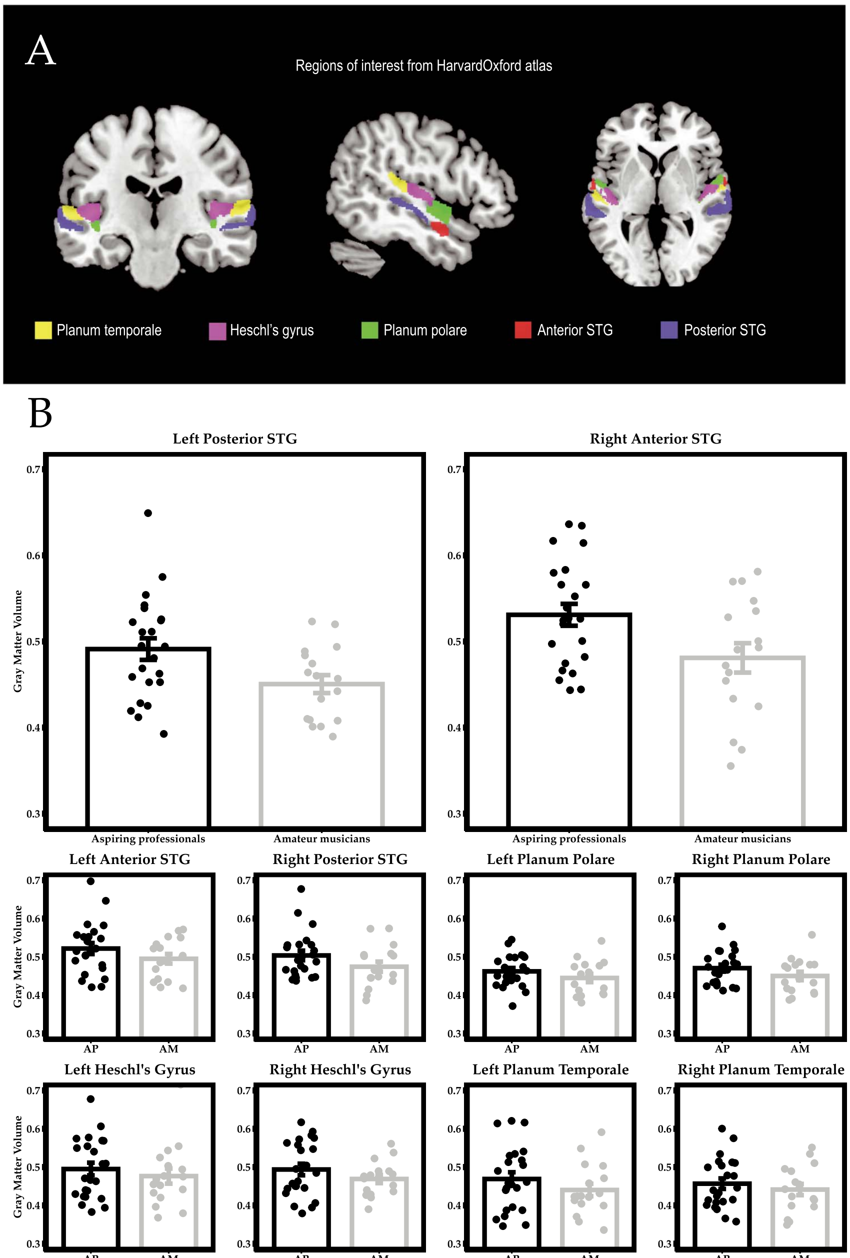

Figure 4. ROI analyses showed a significant difference in GM volume in left posterior STG and right anterior STG ($P < 0.05$). All other ROIs showed the same tendency of greater GM volumes in aspiring professionals than in amateur musicians but failed to reach the threshold of statistical significance.

means that those individuals showing the highest proficiency in this behavioral test were also the ones that exhibited the most pronounced decrease in GM volume. In contrast, the decrease in estimates of GM volumes did not correlate with improvements in music expertise ($r_{\text{planum polare}}$ $(19) = -0.104$, $P = 0.671$; $r_{\text{posterior insula}}$ $(19) = -161$, $P = 0.483$; r_{IFoG} $(19) = -0.171$, $P = 0.483$).

Changes in Functional Connectivity

To understand these changes in GM volume, we further investigated training-dependent changes in the coupling between brain regions. Here, we focused on the largest cluster of structural change located in left planum polare, that is, auditory cortex, and its correlations with other regions of the brain. We found

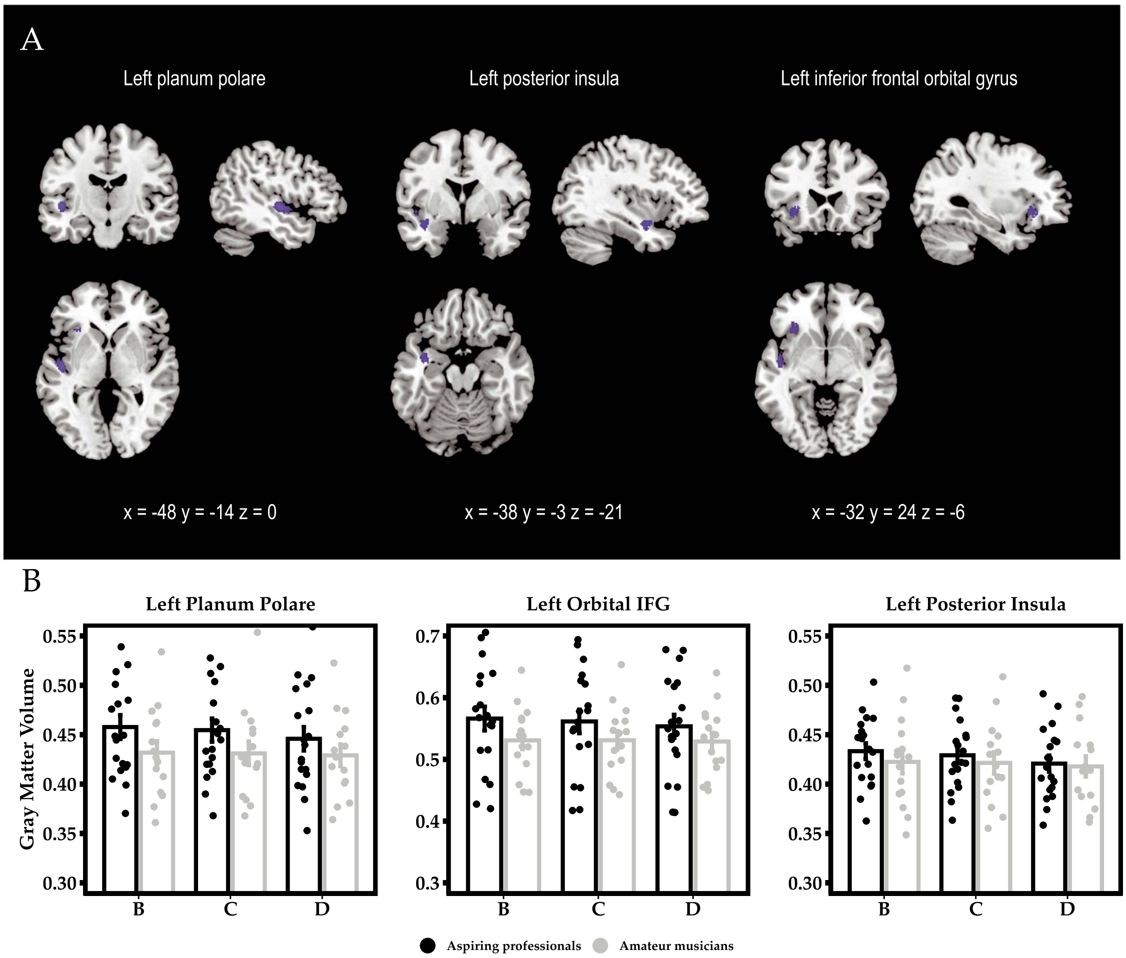

Figure 5. (A) Significant clusters in left planum polare, posterior insula, and IFoG emerging in a whole-brain time-by-group interaction analysis ($P < 0.001$, $k > 47$, corrected for nonstationary smoothness). Coordinates refer to MNI space. (B) Bargraphs with the extracted GM volume estimates of the significant clusters in the time-by-group interaction. This effect is driven by a decrease of GM volume in aspiring professionals compared with amateur musicians. Error bars represent ±1 SE.

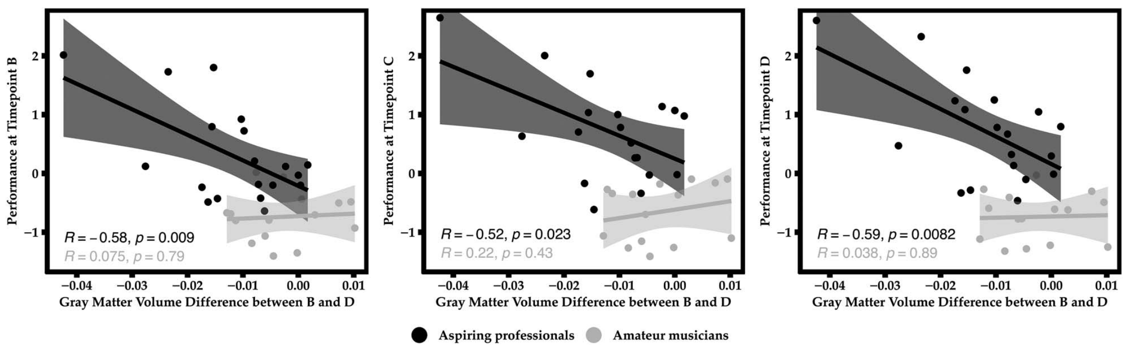

Figure 6. Correlations between decrease in GM volume in left planum polare between time points B and D and behavioral performance in the BGS at measurement occasions B, C, and D, respectively.

increasing functional connectivity of the left planum polare to left and right auditory cortex, left precentral gyrus and left supplementary motor cortex, left posterior cingulate, and left and right postcentral gyrus over time in aspiring professionals compared with amateur musicians (FWE-corrected P value of 0.05; see Fig. 7).

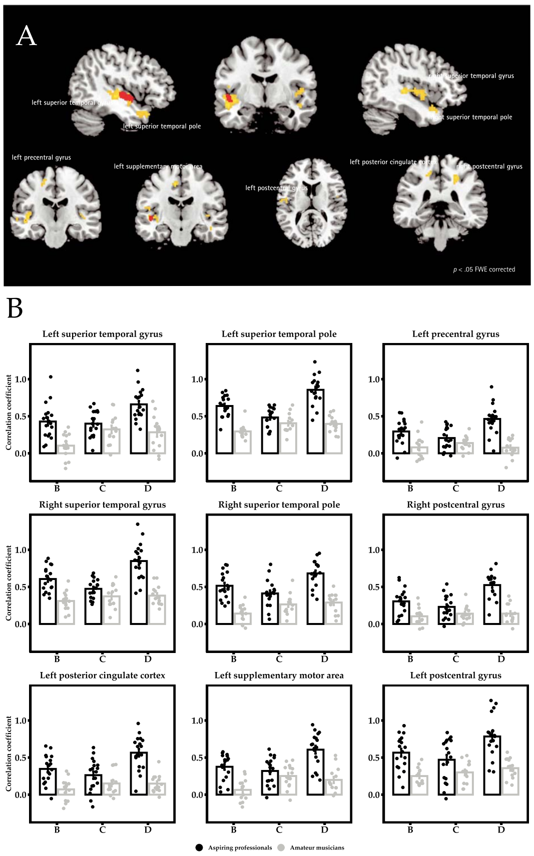

Figure 7. (*A*) Significant clusters exhibiting increased functional connectivity over time (shown in yellow) with left planum polare (shown in red) in aspiring professionals compared with amateur musicians ($P < 0.05$ FWE corrected). (*B*) Bargraphs with the extracted Fisher's z-transformed correlation coefficients from those significant clusters of the time-by-group interaction. Group-by-time interactions of the functional connectivity analysis were driven by increasing correlation coefficients in aspiring professionals relative to stable correlations among amateur musicians. Error bars represent ±1 SE.

Changes in Graph-theoretical Measures

To further characterize the network in which left planum polare participates, we conducted graph-theory analyses and compared network characteristics in the two groups over time. Although there were no significant time-by-group interactions in any of the nodal measures, there were significant time-by-group interactions for all global measures, namely for characteristic path length, global efficiency, local efficiency, and clustering (see Table 3 for exact numbers). In all of those measures, the group of amateur musicians showed no reliable mean change over time, whereas the group of aspiring professionals showed significant increases over time in all global metrics except for path length, which, as expected, decreased over time.

Discussion

In the present longitudinal study, we set out to investigate structural brain alterations and changes in functional connectivity in musicians intensely preparing for their entrance exam at a University of Arts. We found that GM volume decreased over time in comparison to amateur musicians in 3 clusters, namely left planum polare, posterior insula extending into planum polare, and left IFoG extending into anterior insula. The biggest cluster of structural change was observed in left planum polare, which exhibited increased functional connectivity with left and right auditory cortex, left precentral gyrus, left supplementary motor cortex, left posterior cingulate cortex, and left and right postcentral gyrus. All of these regions have been previously identified to play important roles in music expertise (e.g., Luo et al. 2012; Groussard et al. 2014). The increase in connectivity for the region showing the greatest structural change was also reflected in results based on graph theory. Here, we observed changes over time in the global metrics, indicating participation of the planum polare in an increasingly complex network in the group of aspiring professionals compared with amateur musicians.

Our results once again speak to the malleability of adult brain structure to environmental influences (Lövdén et al. 2013; Kühn and Lindenberger 2016; Lindenberger et al. 2017). The left planum polare as a region within the STG, adjacent to left Heschl's gyrus, has been reported to show preferential activity to musical stimuli in comparison to other types of complex sounds, such as speech and nonlinguistic vocalizations, and to integrate acoustic characteristics in the context of complex musical sounds, both in trained musicians and nonmusicians (Angulo-Perkins et al. 2014). In another study, left planum polare showed activity during high-level musical processing (Brown et al. 2004). In a study looking into functional networks underlying music processing and processing of vocalizations with a passive listening stimulation paradigm that included different vocal sound categories (i.e., song, hum and speech), left planum polare together with planum temporale and a group of regions on the right hemisphere that included the supplementary motor area, premotor cortex and the inferior frontal gyrus showed stronger activations during music listening (Angulo-Perkins and Concha 2019). Interestingly, left planum polare also showed activity during vocal musical listening, with and without lyrics, a finding pointing towards its role in music processing of temporally complex sounds, such as vocal music and speech. Overall, evidence suggests that the planum polare might be playing an intermediate role between the primary auditory cortex and other associative cortices, possibly extracting information (such as melodic patterns or pitch-interval ratios) required for further processing leading to perceptual evaluations (e.g., a same-different task), vocal production, and sensory-motor coordination to reproduce melodic or rhythmic sounds (Angulo-Perkins and Concha 2019).

As an integration hub, the insula serves a plethora of different tasks, including sensory, emotional, motivational, and cognitive functions (Gogolla 2017). More specifically within the realm of music, the insula has often been discussed to reflect the emotional aspects of music processing (Blood and Zatorre 2001; Koelsch et al. 2005; Koelsch 2010) and is involved in autonomic regulation and sensory representation of emotion percepts (Koelsch 2014). As aspiring professional musicians do not only have to perfect their technical skills but also have to hone their emotional sensitivity to music, it is conceivable that insula cortex, both anterior and posterior portions, evinces structural change.

Left inferior frontal gyrus is well known for its role in syntactic processing of language and music (Friederici 2002; Tillmann et al. 2006; Nan and Friederici 2012), as well as more broadly in general cognitive functions, such as top-down attention and working memory (Janata et al. 2002; Schulze et al. 2011). Especially the orbitofrontal part has been associated with automatic appraisal

Table 3. Nodal and global measures of graph theoretical analyses at measurement occasions B, C, and D, comparing aspiring professionals to amateur musicians. Asterisks (*) indicate a significant effect.

Nodal measures

	Aspiring professionals			Effect of Time		Amateur musicians			Effect of Time		Time-by-group interaction	
	Time B	Time C	Time D	F	P (FDR-corr.)	Time B	Time C	Time D	F	P (FDR-corr.)	F	P (FDR-corr.)
Degree	98.83	101.16	107.33	8.04	0.011*	99.85	105.21	104.78	2.07	0.241	1.06	0.35
Path length	2.76	2.63	2.21	10.09	0.007*	3.10	2.48	2.91	1.65	0.241	3.06	0.08
Global efficiency	0.42	0.45	0.52	11.30	0.007*	0.37	0.46	0.41	1.51	0.241	3.55	0.08
Local efficiency	1.97	2.24	2.89	12.62	0.007*	1.54	2.28	1.76	2.88	0.241	4.09	0.08
Clustering	0.35	0.39	0.47	11.84	0.007*	0.29	0.39	0.33	3.18	0.241	2.88	0.08

Global measures

	Aspiring professionals			Effect of Time		Amateur musicians			Effect of Time		Time-by-group interaction	
	Time B	Time C	Time D	F	P (FDR-corr.)	Time B	Time C	Time D	F	P (FDR-corr.)	F	P (FDR-corr.)
Characteristic path length	2.89	2.78	2.36	11.15	0.004*	3.15	2.69	2.83	5.52	0.069	4.01	0.02*
Global efficiency	0.40	0.42	0.49	12.79	0.004*	0.36	0.43	0.40	4.57	0.069	5.17	0.02*
Local efficiency	1.84	2.03	2.65	12.39	0.004*	1.47	2.06	1.71	2.62	0.13	7.03	0.01*
Clustering	0.33	0.36	0.44	13.59	0.004*	0.28	0.36	0.34	5.06	0.069	4.002	0.02*

and is activated by breaches of expectancy (Koelsch 2014), a function crucial for aspiring professional musicians, as it helps them to discriminate, for instance, between expected and unexpected chord progressions. Interestingly, there have been findings of projections from the anterior superior temporal plane to the orbitofrontal cortex in rhesus monkeys (Petrides and Pandya 1988), that go along well with a recent finding of functional connectivity of the left planum polare with orbitofrontal cortex in an fMRI study during music-evoked emotional processing (Koelsch et al. 2018).

Within all 3 of these regions, we have found structural decreases in the group of aspiring professionals, while volumes in amateur musicians remained stable. Importantly, we were comparing a group of individuals aspiring to become professional musicians to a group of amateur musicians who actually have a history of comparable years of playing an instrument but with different intensity and a different goal in mind. This stands in contrast to many other studies that have used nonmusicians as a comparison group. All of our participants look back on similar amounts of musical training, but the aspiring professionals presumably have been trying, for quite some time, to perfect their general ear-training skills in order to pass a highly competitive entrance exam. Accordingly, we found some structural differences between aspiring professionals and amateurs at the beginning of our observation period, with aspiring professionals exhibiting more GM volume in hippocampus, superior parietal lobule, superior/middle temporal gyrus, and postcentral gyrus. However, in the following weeks and months, aspiring professionals actually exhibited a decrease of GM volume over time compared with amateur musicians.

At first, the observed decrements in GM volume among aspiring professionals may seem counterintuitive. However, we have argued before that plasticity might in part be characterized by volume expansion followed by a selection process leading to a partial renormalization of overall volume (Wenger et al. 2017a). In fact, given the large number of skills humans acquire during their lifetime, plasticity cannot be conceived as a process of perpetual growth (Changeux and Dehaene 1989; Lindenberger et al. 2017; Wenger et al. 2017b). According to the exploration–selection–refinement (ESR) model of human brain plasticity (Lindenberger and Lövdén 2019; Lövdén et al. 2020) neuronal microcircuits potentially capable of implementing the computations needed for executing novel skills are, early in learning, widely probed, with a concomitant increase in GM volume. This phase of exploration is followed by phases of experience-dependent selection and refinement of reinforced microcircuits and the gradual elimination of novel structures associated with unselected circuits. It is tempting to speculate that the aspiring professionals had entered the selection and refinement phases of a plastic episode when they were recruited for participation in the present study. Clearly, this interpretation needs to remain tentative because we did not observe the full cycle of volume expansion followed by renormalization as in our previous study on motor training (Wenger et al. 2017b) or as Quallo et al. (2009) did in their study on tool-use in monkeys. Nevertheless, it offers a tenable explanation for the observed structural decreases in left planum polare, posterior insula, and IFoG that needs to be corroborated in future work.

Thus far, data that are consistent with the ESR model have been primarily observed in early ontogeny or during motor skill acquisition; for review, see Lindenberger and Lövdén (2019). Acquiring a complex skill like playing an instrument, in combination with mastering the complexities of harmony and ear training is a different story. There are no data available yet that chart the sequential progression of plasticity over years of musical training. What is documented in the literature are, for the most part, cross-sectional studies showing differences in brain structure between musicians and nonmusicians. We can therefore only speculate how the alteration of brain structure in response to years of musical training that has evidently resulted in lasting volume expansion can be reconciled with an ESR view of plastic change. One possibility is that changes occur as a sequence of several expansion–renormalization cycles that always conclude in only partial renormalization. This would in the long run result in a building-up of consistently "skill-optimized" GM structure. Obviously, we could not investigate this hypothesis in the current study. What we have observed is a decrease in estimates of GM volume in the group of musicians intensely preparing for an entrance exam, in comparison to a group of musicians still actively performing music on a daily basis but without intensive training. It is noteworthy that others have reported associations between smaller volume and higher expertise: In ballet dancers (Hänggi et al. 2010) and also in skilled pianists (Granert et al. 2011), striatal volume was smaller in individuals with greater motor function efficiency. Furthermore, in a study investigating nonmusicians, amateurs, and expert musicians, there was a negative correlation between degrees of music expertise and GM density in right postcentral gyrus, bilateral precuneus/paracentral lobule, left inferior occipital gyrus, and bilateral striatal areas (James et al. 2014).

Following up on our structural results, we also investigated whether we would see indications of plasticity at the functional level. If what we observed here is indeed the second part of an expansion–renormalization cycle, then the left planum polare, which made up the largest patch of GM showing volume reduction, would be expected to undergo changes in functional connectivity. Hence, we expected that the planum polare would show increased connectivity throughout the brain, specifically to regions previously implicated in musical processing. Indeed, resting-state functional connectivity analyses revealed that over time, the left planum polare was better connected within left auditory cortex itself extending towards superior temporal pole, and also to the right auditory cortex and superior temporal pole, left precentral and also supplementary motor area, left posterior cingulate cortex, and left and right postcentral gyrus, regions that have been shown before to matter in music expertise (Luo et al. 2012; Groussard et al. 2014).

Left auditory cortex has been shown to be involved in processing of melody (Bengtsson and Ullén 2006) and more specifically also in musical semantic memory (Groussard et al. 2010). Left posterior cingulate cortex has been discussed in the context of integrating sensory information and emotional content, for example during reading musical notation (Hyde et al. 2009), in the context of familiarity tasks featuring well-known songs (Satoh et al. 2006), and in combination with autobiographical memories associated with musical excerpts (Ford et al. 2011). Supplementary motor area has been shown before to exhibit greater GM volume in musicians versus nonmusicians (Gaser and Schlaug 2003) and has been implicated in the processing of sequential temporal structures (Bengtsson et al. 2009), pitch and timing repetition during both listening and performance tasks (Brown et al. 2013), as well as in rhythmic and melodic musical improvisation (de Manzano and Ullén 2012).

Also, the results of our graph theoretical analysis go along with our assumption that the region of decreased volume exhibits improved functionality after restructuring and indeed point to the fact that planum polare is now participating in a more complex network. This is reflected in all global measures of graph complexity we investigated, but not on the nodal level.

At all measurement occasions, we observed significant correlations between individual differences in GM volume decrements and music expertise. In other words, the highest performing individuals exhibited the most pronounced decreases in GM volume in left planum polare, left insula, and left inferior frontal gyrus, thus, show the largest plastic change on the neural level. However, counter to expectations, we did not observe any significant correlations between changes in music expertise and changes in GM volume. One reason for the absence of such a change–change association is the high degree of stability of individual differences in music expertise over time. For instance, in aspiring professionals, we observed the following correlations in music expertise between adjacent measurement occasions ($r_{AB} = 0.955$; $r_{BC} = 0.896$; $r_{CD} = 0.950$; $r_{DE} = 0.981$).

We can only speculate about the neurobiological mechanisms that may have caused the observed reductions in GM volume. Synaptic changes including dendritic branching and axon sprouting as well as glial changes come to mind and we and others have elaborated on the exact potential mechanisms before (Zatorre et al. 2012b; Wenger et al. 2017a; Lindenberger and Lövdén 2019). Future studies need to incorporate additional MR sequences specifically tailored to disentangle these processes, as for example T_1 maps (Tardif et al. 2016; Lerch et al. 2017).

The present study also has some further limitations that need to be mentioned. First, there was no random assignment of participants to groups. Obviously, this caveat is inherent in the studied topic and is not easy to overcome. We have tried to limit this problem by recruiting two groups of participants with comparable years of playing an instrument. Still, there might be pre-existing differences between people who aspire to become professional musicians and people who consider themselves amateur musicians (Ullén et al. 2016). In addition, the stress to which aspiring professional musicians are exposed might have influenced the present results, as stress has been shown to result in GM volume reductions (Kassem et al. 2013). Thus, we cannot rule out that the observed decreases in GM volume might, to some extent, be related to stress, even though our findings of increased functional connectivity and the correlation with behavioral performance renders this explanation rather unlikely, and also auditory cortex does not belong to those regions typically affected by stress-related reductions (Lupien et al. 2009). Finally, the present samples were not systematically stratified by which main instrument the participants played. Hence, we may have missed out on effects that are specific to particular focal instruments, such as piano versus strings.

To conclude, we found that musicians intensely preparing for the entrance exam to a University of the Arts show reliable reductions in GM volume in regions pertinent to music expertise, whereas a group of amateurs not preparing for an exam did not show such changes. The planum polare, which was the largest GM cluster with volume reductions, showed increasing functional connectivity to other musically relevant regions. This increase in connectivity was also reflected in global metrics of network participation based on graph theory. The present results are consistent with the ESR model of plastic change (Lindenberger and Lövdén 2019; Lövdén et al. 2020), which posits an expansion of GM volume during early phases of skill acquisition, followed by partial renormalization (Wenger et al. 2017a).

Supplementary Material

Supplementary material can be found at *Cerebral Cortex Communications* online.

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Notes

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13 Appendix B

Biographical statement

Education	**Candidate for Doctor of Philosophy in Psychology**	Oct. 2018-Febr. 2023
	Max Planck Institute for Human Development, *Berlin, Germany* The International Max Planck Research School on the Life Course, *Berlin, DE* Dissertation: *Experience-dependent plasticity in the auditory domain: effects of expertise and training on functional brain organization*	
	Master of Science in Social, Cognitive, and Affective Neuroscience	Oct. 2014 – July 2018
	Freie Universität Berlin, *Berlin, Germany* Thesis: *Language Network in rest: a multimodal functional connectivity approach*	
	Bachelor of Arts (Honours) in Philology with specialization in Linguistics	Sept. 2009 – Sept 2014
	Aristotle University of Thessaloniki, *Thessaloniki, Greece*	
Honors and awards	Scholar by German Academic Exchange Service (DAAD)	2015-2016
Experience	**Student assistant**	Jan. 2017 – Sept 2018
	Max Planck Institute for Human Development, *Berlin, Germany* Mechanisms and Sequential Progression of Plasticity Cognitive and Neural Dynamic of Memory Across the Lifespan	
	Student assistant and intern	May. 2015 – Sept 2018
	Neuroimaging Group at Experimental and Clinical research center (ECRC), Dept. of Anesthesiology, Charité-Universitätsmedizin, *Berlin, Germany* Project: *Biomarker Development for Postoperative Cognitive Impairment in the Elderly*	
Papers	Wenger E., **Papadaki E.**, Werner A., Kühn S., & Lindenberger U. (2021). Observing Plasticity ofthe Auditory System: Volumetric Decreases Along with Increased Functional Connectivity in Aspiring Professional Musicians. *Cerebral Cortex Communications, 2(2), 1–14.* https://doi.org/10.1093/texcom/tgab008	2021 (in press)
	Papadaki E., Koustakas T., Werner A., Lindenberger U., Kühn S., & Wenger E. (2022). Resting state functional connectivity in an auditory network differs between aspiring professional and amateur musicians and predicts performance.	2023 (under review)
Conferences	LaP meeting-Learning and Plasticity, *Lapland, Finnland*	April 2022