OXFORD

Psychoradiology, 2023, **3**, 1–8

DOI: 10.1093/psyrad/kkad003

Advance access publication date: 2 March 2023

Research Article

Resting-state functional connectivity in lifelong musicians

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Abstract

Background: It has been postulated that musicianship can lead to enhanced brain and cognitive reserve, but the neural mechanisms of this effect have been poorly understood. Lifelong professional musicianship in conjunction with novel brain imaging techniques offers a unique opportunity to examine brain network differences between musicians and matched controls.

Objective: In this study we aim to investigate how resting-state functional networks (FNs) manifest in lifelong active musicians. We will evaluate the FNs of lifelong musicians and matched healthy controls using resting-state functional magnetic resonance imaging.

Methods: We derive FNs using the data-driven independent component analysis approach and analyze the functional network connectivity (FNC) between the default mode (DMN), sensory-motor (SMN), visual (VSN), and auditory (AUN) networks. We examine whether the linear regressions between FNC and age are different between the musicians and the control group.

Results: The age trajectory of average FNC across all six pairs of FNs shows significant differences between musicians and controls. Musicians show an increase in average FNC with age while controls show a decrease ($P = 0.013$). When we evaluated each pair of FN, we note that in musicians FNC values increased with age in DMN–AUN, DMN–VSN, and SMN–VSN and in controls FNC values decreased with age in DMN–AUN, DMN–SMN, AUN–SMN, and SMN–VSN.

Conclusion: This result provides early evidence that lifelong musicianship may contribute to enhanced brain and cognitive reserve. Results of this study are preliminary and need to be replicated with a larger number of participants.

Keywords: resting-state fMRI; lifelong musicianship; default mode network; sensory-motor network; functional network connectivity; cognitive reserve

Introduction

There is a significant body of research devoted to understanding the interaction of high-end cognitive demands on the building of cognitive reserve across the lifespan with effects that span both healthy aging and pathology. These studies often focus on bi-and multi-lingualism with a lesser body focusing on musicianship, and include a variety of structural and functional neuroimaging techniques at the cortical and subcortical levels (Pantev *et al.*, 2001; Munte *et al.*, 2002; Coggins *et al.*, 2004; Bangert *et al.*, 2006; Bermudez *et al.*, 2009; Jancke, 2009; Oechslin *et al.*, 2009; Wan and Schlaug, 2010; Halwani *et al.*, 2011; Luk *et al.*, 2011; Kuhnis *et al.*, 2013; Abutalebi *et al.*, 2015; Abutalebi, Guidi *et al.*, 2015; Pliatsikas *et al.*, 2015; Weiss and Bidelman, 2015; Yuskaitis *et al.*, 2015; Felton *et al.*, 2017; Andrews *et al.*, 2021).

The neuroimaging studies of musicians and musicianship is a burgeoning field of inquiry that emerged in the early 2000s (Pantev *et al.*, 2001; Munte *et al.*, 2002; Bangert *et al.*, 2006; Jancke, 2009; Elmer and Jancke, 2018). Recent work on musicians, especially diffusion tensor imaging (DTI) analysis of white matter tracts, has contextualized imaging analysis within the framework of aging and building cognitive reserve (Oechslin *et al.*, 2009; Halwani *et al.*, 2011; Andrews *et al.*, 2021). Although early evidence suggests enhanced generation of neuronal, dendritic, and synaptic connections and functional reorganization of neural networks across modalities, the case that the neural mechanisms of musicianship can lead to enhanced brain and cognitive reserve is not well understood and requires further investigation.

Neuroimaging research focusing on professional musicians can be categorized into the following main topics: (i) the relationship of musicianship and neuroplasticity (Munte *et al.*, 2002; Jancke, 2009), (ii) neuroanatomical correlates of musicianship (Pantev *et al.*, 2001; Bermudez *et al.*, 2009), (iii) enhanced encoding of vowels and speech in professional musicians (Kuhnis *et al.*, 2013; Weiss and Bidelman, 2015), (iv) timbre-specific auditory cortical representations in musicians (Kuhnis *et al.*, 2013), (v) shared networks for auditory and motor processing in professional musicians (Bangert *et al.*, 2006), and (vi) brainstem recordings of speech sounds in musicians (Weiss and Bidelman, 2015). These topics have been investigated using various functional and structural magnetic resonance imaging techniques (MRI). Resting-state functional MRI (rfMRI) focusing on musicians began to emerge more recently and have been limited to studies of improvization (Bengtsson *et al.*, 2007; Ansari, 2008; Berkowitz and Ansari, 2008; Berkowitz and Ansari, 2010; Rosen *et al.*, 2016; Lopata *et al.*, 2017), different types of musical training (Belden *et al.*, 2020), and more general musical creativity (Bashwiner *et al.*, 2020).

Received: 1 December 2022; **Revised:** 30 January 2023; **Accepted:** 24 February 2023

These studies apply region of interest (ROI) seed-based analysis approaches.

Raichle's important work on intrinsic brain activity based on resting-state fMRI (rfMRI) have proven to be very significant in increasing the depth of understanding the baseline functional networks (FNs) of the human brain. In rfMRI, participants do not perform an assigned task, but are asked to lie still, stay awake, and relax (Biswal *et al.*, 1995; Lowe *et al.*, 1998). Numerous studies have reported that rfMRI data are associated with age, neural response, fluid intelligence, sex, genetics, and many mental disorders (Greicius *et al.*, 2004; Craddock *et al.*, 2009; Dosenbach *et al.*, 2010; Glahn *et al.*, 2010; Scheinost *et al.*, 2014; Finn *et al.*, 2015; Zhang *et al.*, 2016; Canario *et al.*, 2021). In this study, we investigate how FNs of rfMRI are associated with musicianship. Studies have suggested that the baseline FNs of the brain are not constrained by the underlying anatomical white matter connections observed through DTI (Raichle, 2011; 2015). Underlying mechanism of FNs are complex and includes the spontaneous rfMRI fluctuations and their correlation to each other (He *et al.*, 2008; He and Raichle, 2009). Raichle's rfMRI studies provide a clear basis set of FNs resulting from the intrinsic fluctuations in brain activity that consist of bilateral, symmetrical, and discrete cortical areas, including the default mode (DMN), the sensorimotor (SMN), auditory (AUN), visual (VSN), executive control (ECN), dorsal attention (DAN), and salience networks (SN) (Raichle, 2011). In this study, we focus on these primary baseline FNs of rfMRI and calculate the functional network connectivity (FNC) between the FNs in lifelong musicians and matched controls.

With regard to cognitive brain reserve and cognitive flexibility: it should be noted that the distinctions between the terms used to characterize different types of brain reserve. Neurological (brain) reserve, one of the earliest terms proposed (Valenzuela and Sachdev, 2006) is generally considered to be more biologically and genetically based, with two main definitions:

(i) "The neurological brain reserve hypothesis proposes that individuals generally differ in the numbers of neurons and synapses available to be lost before clinical symptoms emerge." (Stern, 2012).
(ii) "Brain reserve refers to 'passive' factors (e.g. brain volume, synapse count) that confer a particular capacity to endure neuropathological processes until a critical threshold is reached, after which cognitive and functional impairments are expressed." (Guzman-Velez and Tranel, 2015).

By contrast, cognitive reserve, also called behavioral brain reserve, is acquired through specific sensory–motor activities that span across the life cycle (including but not restricted to musicianship and bilingualism). This type of cognitive brain reserve is considered "resilience to neural insult" and strategies that strengthen alternative FNs across the life cycle can improve tolerance of atrophy (Bialystok *et al.*, 2007). Moreover, higher cognitive reserve should require more structural decline for symptoms to manifest (Gold *et al.*, 2013). For more discussion on cognitive reserve, see Craik *et al.* (2010), Andrews *et al.* (2013; 2021), Andrews (2014), and De Bot *et al.* (2020).

Another body of research that is relevant in the context of the current analysis focuses on enhanced cognitive flexibility. Studies involving cognitive flexibility have included a range of cohorts as well as different types of development, including the trajectory of learning in infants who are raised in bilingual environments (Kovacs and Mehler, 2009), studies of the neurophysiological correlates of flexibility (Mastria *et al.*, 2021), correlates of network flexibility and functional connectivity (Betzel *et al.*, 2014), and specific efforts to identify connections with neural substrates and specific networks (e.g. executive control, default mode and others) (Dajani and Uddin, 2015). We will return to the notions of cognitive reserve and cognitive flexibility in the Discussion section.

This study is novel in two main ways. First, musicians included in this study are lifelong musicians with many years of musical training and experience, and currently practicing music multiple hours per week. This is a rare cohort and to our knowledge this level of musicianship has not been investigated in previous studies. Second, we apply a data driven approach called independent component analysis (ICA) (Bell and Sejnowski, 1995) where analyses are not limited to *a priori* ROI. Limiting analyses to known ROI can miss brain regions that are relevant to musicianship and important hubs of the FNs may not be fully characterized. ICA uncovers FNs that are relevant to the rfMRI data obtained from study participants by applying spatial independence between FNs. FNC, or the temporal correlations between the FNs identified by ICA, is evaluated to understand brain function at the systems level. We expect to see FNC differences between the musicians and age matched controls in FNs that are relevant to musicianship, namely the DMN, AUN, SMN, and VSN. Each of these FNs is clearly identified in our rfMRI dataset of 16 participants (eight musicians and eight non-musicians). In addition, we examine how FNCs between these FNs change across the lifespan. We predict that the FNC between these FNs will increase with age in musicians.

Materials and Methods

Participants

Sixteen participants (eight musicians and eight non-musician controls) gave written consent in accord with the guidelines of Duke Health Institutional Review Board. All participants were MRI scanned in 2019–2021 at Duke University Hospital at the Duke Brain Imaging and Analysis Center:

Musicians were between the ages of 20 and 67 years, with a mean age of 44.1 years (five females and three males) and controls were between the ages of 20 and 63 years, with a mean age of 43 years (five females and three males). Participants in both groups have college degrees that span the baccalaureate (completed or in progress) through the MA or MS and PhD, and one with an Associate's degree.

All eight musicians began musical training between the ages of 3 and 12 years, at an average age of 6.4 years. The number of years the participants had been musicians was a correlate of chronological age since all were currently active musicians, performing regularly with an average of 38 years of active musicianship. Musicians reported an average of 3 hours per day rehearsing and/or practicing and an average of 9 hours per day in peak times (i.e. during periods of performance). Additional credentials included college degrees in music (including undergraduate minor, master's, and doctorate) and multiple affiliations with orchestras, symphonies, or operatic theatres in the USA and abroad. Five of the professional musicians had extensive experience in the USA and abroad. All participants played at least the piano or violin. The eight non-musician control participants do not play any instruments and do not sing in any groups. Four of the eight have never played a musical instrument, three played in high school between 14 and 18 years of age, and one played for 6 months at the age of 14. This yields a mean of 35 years since any of the controls were actively involved in playing a musical instrument.

Image acquisition

All participants were scanned in the same scanner at Duke University Hospital, using a GE 3T Discovery 750 MRI (General Electric, Milwaukee, WI, USA) with an eight-channel head coil. Anatomical T1-weighted images were acquired, using a FSPGR sequence, with an echo time (TE) = 2.9 ms, repetition time (TR) = 7.6 ms, inversion time (TI) = 450 ms, flip angle of 12°, with an reconstructed image size of 256 × 256 × 162 and a voxel size = 1.0 × 1.0 × 1.0 mm^3. The functional imaging sequence was an interleaved T2∗ weighted echoplanar (EPI) sequence with 34 axial slices that were 4 mm thick, with a flip angle = 90°, TE = 30 ms, and a 64 × 64 in-plane matrix with a 24 cm field of view. A total of 155 time points were acquired per participant with a TR of 2000 ms.

Image processing

The structural brain images were skull stripped and normalized to MNI using Advanced Normalization Tools (ANTs) (Avants *et al.*, 2011). Functional images were preprocessed using the FMRIB Software Library (FSL) (Smith *et al.*, 2004; Woolrich *et al.*, 2009; Jenkinson *et al.*, 2012) with the exception of the registration step. All functional images were preprocessed using the FMRI Expert Analysis Tool (FEAT, a part of FSL), including slice time correction, motion correction, high pass filter above 0.01 Hz, and registration from functional space to native structural space. All registrations from native structural space to MNI were performed using ANTs, including for functional images. All participants' fMRI masks were combined into a group mask, using a voxel-wise logical 'AND' operator for all 16 participants. This group mask was used for all participants before running GIFT (Calhoun *et al.*, 2004; Calhoun *et al.*, 2004). GIFT was run as a standard ICA to estimate 20 independent components (networks), using the Infomax algorithm (Bell and Sejnowski, 1995). The 20 components were further reduced first by excluding the artefactual FNs and then selecting the rfMRI FNs that matched previous literature (Raichle, 2011; 2015). We then picked four FNs (DMN, AUN, SMN, and VSN) for further analysis as they have been implicated as being related to musical skills according to previous literature on musicianship (Bangert *et al.*, 2006; de Aquino *et al.*, 2019; Belden *et al.*, 2020). To ensure that motion is not driving FNC, FN time courses from the GIFT software were nuisance regressed using MCFLIRT's six motion parameters. This regression was done using MATLAB's regstats function (MATLAB v.9.1 and Statistics Toolbox v.12.1, MathWorks, Natick, MA, USA). The FNC between pairs of FNs was calculated by computing the temporal correlation between their time courses output by the ICA algorithm. The correlation between FN time courses was computed using MATLAB's corrcoef function. Finally, the FNC matrix between the four FNs of interest was constructed using the correlation between the FN pairs.

Statistics

This study examines whether the linear regressions between FNC and age are different between the musicians and the control group. We compare the slope difference between the two groups for each pair of FN using a test for parallelism (Kleinbaum *et al.*, 2013). Two-sided tests were performed for all FN pairs. Then we combine the *P* values for all FNs using Fisher's method (Fisher, 1992). As FNs within the same subject may be dependent, we adjust Fisher's pooled test for such dependence by using a method to calculate the effective number of tests as given by Li and Ji (2005). The adjustment uses the poolr R software package written by Ozan Cinar and Wolfgang Viechtbauer. *P* values below a threshold of 0.05 are considered to be statistically significant.

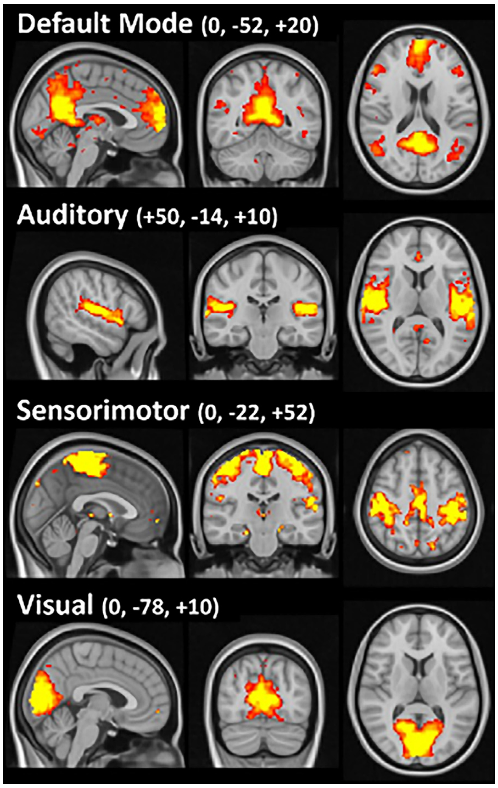

Figure 1: The sagittal, coronal, and axial views of the default mode (DMN), auditory (AUN), sensorimotor (SMN), and visual (VSN) networks derived from rfMRI of musicians and controls. The networks displayed are the group averages across all participants and are in the MNI152 space (MNI coordinates of these views are in parentheses).

Results

The DMN, AUN, SMN, and VSN derived using rfMRI data of both musicians and controls using the GIFT toolbox are presented in Fig. 1. These FNs were selected based on the spatial similarity of these FNs with the FNs in Raichle's original work (Raichle, 2011). The FNs presented in Fig. 1 are group averages across all participants.

We then calculated the FNC values between the time courses of the four FNs for each participant. For each participant, a total of six FNC values (pairs of two from the four FNs) were calculated. The average FNC values for the musicians and controls are presented in Table 1. We then performed a two-sided two-sample *t* test on FNC values between the musician and control groups. We found a statistically significant ($P = 0.02$, uncorrected for multiple testing) FNC group difference between the musicians and controls between the DMN and VSN. We also note that for all six FNC values the musicians had a lower average FNC value compared to the controls.

FNC values presented in Table 1 are presented in Fig. 2 as connectograms. The average FNC values for each group, as well as the *t*-value of group difference, are represented by the color of the line connecting the FNs. The darker colors in the control group denote higher FNC values in controls.

The FNC values reported in Table 1 and Fig. 2 are group averages across a wide age range. We examine the effect of age in Fig. 3. In Fig. 3, we plot the mean FNC of all six FNC pairs for each participant against their age. We note that the slope of the musicians' regression line is positive and that of controls' is negative, indicating that FNC in musicians increased with age, whereas FNC in

Table 1: Average group FNC of musicians and controls and FNC difference between the groups

FN pair	FNC musicians average ± SD (range)	FNC controls average ± SD (range)	Musicians vs. controls t value	P value (uncorrected)
DMN–AUN	0.01 ± 0.29 (−0.26, 0.59)	0.16 ± 0.18 (−0.14, 0.41)	−1.248	0.232
DMN–SMN	−0.07 ± 0.20 (−0.34, 0.28)	0.19 ± 0.32 (−0.20, 0.67)	−1.946	0.072
DMN–VSN	0.09 ± 0.29 (−0.38, 0.55)	0.42 ± 0.21 (0.18, 0.76)	−2.572	0.022
AUN–SMN	0.02 ± 0.31 (−0.45, 0.46)	0.08 ± 0.40 (−0.60, 0.68)	−0.377	0.712
AUN–VSN	0.36 ± 0.15 (0.14, 0.58)	0.49 ± 0.12 (0.24, 0.61)	−2.007	0.065
SMN–VSN	0.13 ± 0.21 (−0.09, 0.61)	0.33 ± 0.39 (−0.25, 0.69)	−1.258	0.229

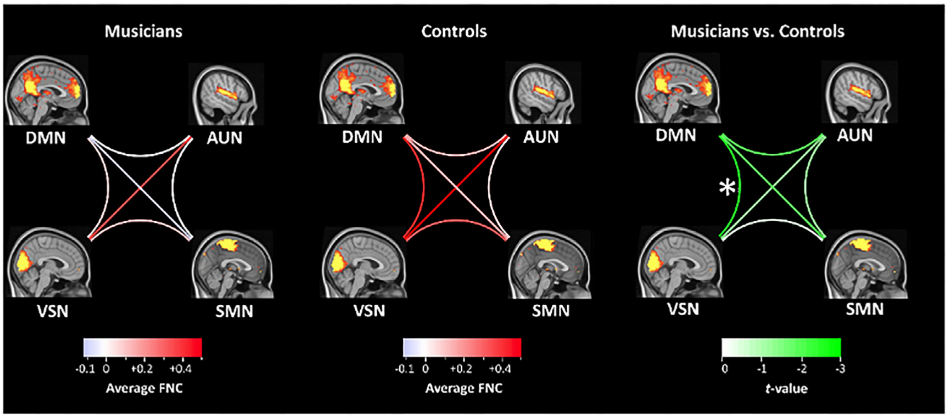

Figure 2: Average FNC in musicians, controls, and musician versus control differences for all pairs of FNs. The FNC value between each network pair is depicted by the connecting line color. The asterisk denotes a statistically significant (uncorrected) FNC difference between the musicians and controls.

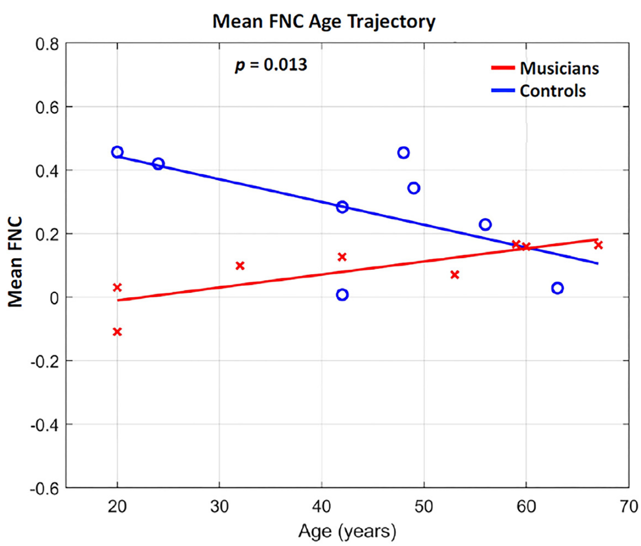

Figure 3: Simple linear regression between mean FNC and age for the musician (red) and control (blue) groups. Mean FNC was calculated across all six FNC pairs. Each open circle is a control participant measure, and each cross is a musician measure. The slopes of the two regressions are significantly different ($P = 0.013$).

controls decreased with age. Linear regression analysis was performed with FNC as the dependent variable and age as the independent variable. The test for parallelism indicated that the slopes of the musician and control groups were significantly different ($P = 0.013$, two-sided).

In Fig. 4 we plot the FNC trajectories for each of the six FNCs. We note that FNC values are decreasing in controls with age in the DMN–AUN, DMN–SMN, AUN–SMN, and SMN–VSN; are stable in AUN-VSN; and increase in DMN–VSN. In musicians, FNC values are increasing with age in DMN–AUN, DMN–VSN, and SMN–VSN; are stable in DMN–SMN and AUN–SMN; and decrease slightly in AUN–VSN. In summary, the musicians generally show increasing FNC with age, and the controls generally show a decreasing trend. When the test for parallelism was applied on the regression lines to evaluate the statistical significance of group interaction, we note that the group interaction for the AUN–SMN was statistically significant ($P = 0.03$, uncorrected) and for DMN–AUN and DMN–SMN group interactions were approaching significance.

Using the SAS (SAS Institute Inc., Cary, NC, USA) *F* test, we pooled equations to test for parallelism (Kleinbaum *et al.*, 2013) across all six FNC pairs. We combined the six network pairs using Fisher's method and adjusted for dependence as explained in the Methods section. The dependence analysis estimated the effective dependence in the dataset by calculating the empirical 6×6 correlation matrix from all FNC values of Fig. 4 (six FNC pairs across all 16 participants). We then used the poolr function meff, and the standard pooling technique for dependent *P* values (Li and Ji, 2005). The meff function used the correlation matrix and found that the effective number of tests or dependence was five (out of six, which is the case of full independence). With this adjustment of the pooled *P* values, the combined *P* value equals 0.0389.

Discussion

In this study, we find that musicians have increasing FNC with age compared to matched control participants. Using ICA, as is done in the Allen *et al.* (2011) study, we find a decrease in FNC with age in four of the six FN pairs in control participants, and an increase in FNC in three of the six pairs in musicians. The

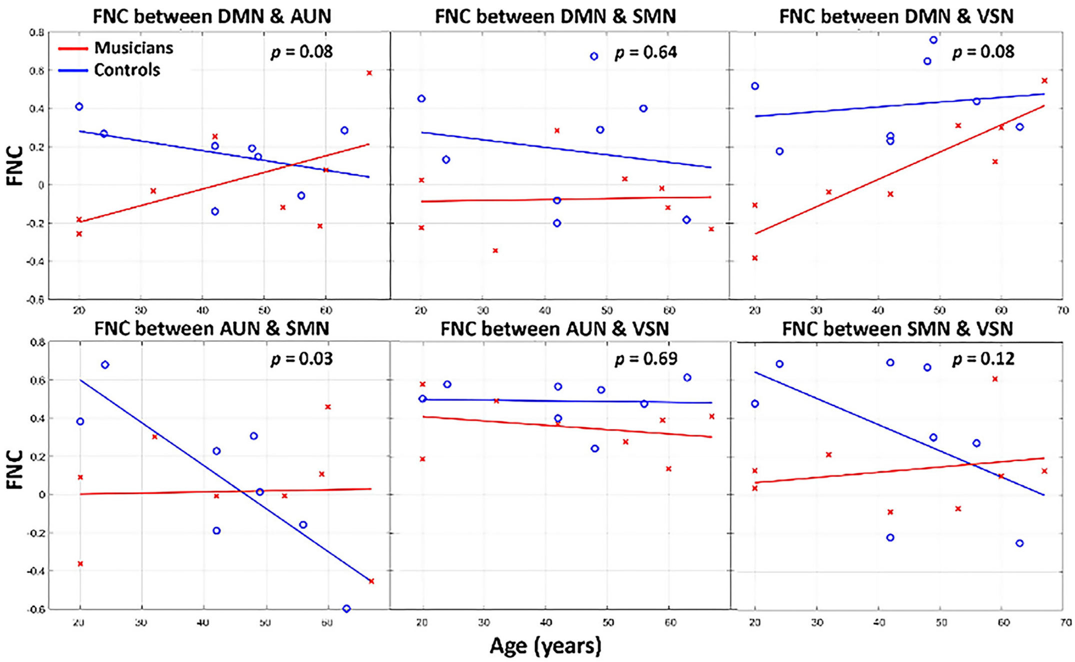

Figure 4: Age trajectory of FNC for six FNC pairs, musicians in red crosses and controls in blue circles. *P* values denote the statistical significance of interaction terms between the groups.

only exception is a very slight increase in controls in the DMN–VSN FNC and a dramatic increase in the musicians. Further, we find that the average FNC across all six pairs of FNs increases with age in musicians and decreases in controls. This finding could be important in terms of musicianship and building cognitive reserve, and argue that the aging effect on FNC experienced by the controls may be enhanced or at least mitigated in musicians.

There are important studies that have examined changes in structural and functional connectivity in healthy aging with findings that are relevant to current work. Allen *et al.* (2011) focused on the important question of determining baselines for comparison of rfMRI FNs using ICA. They analyzed 603 healthy participants ranging in age from 12 to 71 years. Their cross-sectional study showed that FNC decreased in older participants. In Zhang *et al.* (2016) the decrease in FC with age was evident even in early adulthood (22–36 years). In Zhang *et al.* (2016), close to 500 healthy individuals from the human connectome project were investigated using an ROI approach and the age effect on FC was significant even after controlling for cognitive measures. These two studies indicate decrease in FC both between FNs, as well as between ROI applying two different analytic approaches. Ferreira and Busatto (2013) conducted a meta-analysis and summarized results from rfMRI studies that focused on aging-related FC. They noted a significant increase in neuroimaging studies that examined the effects of aging on rfMRI since 2009 that corresponds to the body of evidence arguing for the importance of examining intrinsic brain activity in healthy function. They reported that findings consistently showed a decreased FC in the DMN, as well as attention networks, SMN, and others. On the other hand, they referred to studies that found increased FC in motor and subcortical networks, suggesting that age-related FC changes may be different between motor and subcortical networks, in contradistinction to the DMN and attention FNs (Tomasi and Volkow, 2012). Betzel *et al.* (2014) examined rfMRI in aging and included FCs both within and between FNs. Using the public data from the Nathan Kline Institute, 126 participants from 7–85 years of age were included. Their results indicated an interpretation of decreasing FC within FNs and increasing FC between FNs.

Betzel *et al.* (2014) also noted that there is compelling evidence that structural connectivity and FC are related, where structural connectivity may cause changes in FC patterns (Betzel *et al.*, 2014). Our recent DTI study of subcortical white matter fiber tracks in musicians (Andrews *et al.*, 2021), indeed showed that the structural integrity of white matter tracts was higher in musicians. In that study, we found that fractional anisotropy (FA) values the superior longitudinal fasciculus and the uncinate fasciculus were higher in lifelong musicians compared to matched controls. The same was also true in the bilateral SS, a tract important for bilingualism. The results of this DTI study also suggested that lifelong musicianship may affect the expected decrease in FA values in these subcortical tracts, and, in fact, lead to greater integrity in aging. In sum, the trajectories of FA in the DTI study and FC in the current rfMRI follow a similar pattern in both musicians and controls. These studies may indicate that function follows form, and future studies are needed to confirm the reproducibility of this finding.

Previous studies that focus on creativity and improvization in musicians are all ROI seed-based analyses. Our study is unique as it examines FC between different networks in lifelong highest proficiency musicians and matched controls who have very little or no musicianship. The current study applies a data driven approach where analyses were not limited to *a priori* ROI. As noted before, limiting analyses to known ROI may fail to take into account brain regions that are relevant to musicianship and fail to include these brain regions in relevant networks. An interesting point to note is in the differences in FNC in musicians and controls at the younger end of the spectrum at around 20 years. de Aquino *et al.* (2019) suggested that musicians have less activation in the DMN than nonmusicians. It is unclear whether lesser DMN activation led to decreased DMN FNC and this question merits future research.

Another body of research that is relevant in the context of the current analysis focuses on enhanced cognitive flexibility. Studies involving cognitive flexibility have included a range of cohorts as well as different types of development, including the trajectory of learning in infants who are raised in bilingual environments (Kovacs and Mehler, 2009), studies of neurophysiological correlates of flexibility (Mastria *et al.*, 2021), correlates of network flexibility and FC (Betzel *et al.*, 2014), and specific efforts to identify connections with neural substrates and specific networks (e.g. executive control, default mode and others) (Dajani and Uddin, 2015). Our results indicate that the younger musicians in our group of participants show lower FNC compared to their age matched controls. It is unclear whether this phenomenon can be attributed to higher cognitive flexibility and this question warrants further investigation.

Early and current research on the building of cognitive brain reserve has focused primarily on bilingualism and other specific, high-end cognitive demand activities and lifestyles that may play a role in building cognitive brain reserve, including volume changes in gray matter and white matter, increased structural connectivity, enhanced categorical perception, and a potential protective effect in delaying the onset of symptoms of pathology and dementia. Studies of cognitive reserve in musicians also show similar findings given in the literature on bilingualism. It has been shown in multiple studies that white matter integrity decreases in normal aging, which provides a background for understanding the differences seen in research of building cognitive reserve (see previously), where the process of loss of integrity of white matter fiber tracts can be slowed down or changed by lifelong bilingualism and musicianship. In the current study, we explore how FNC between four FNs (DMN, AUN, SMN, VSN) important in musicianship show an increase in musicians and a decrease in controls. Preliminary findings from the study suggest a possible interaction between structural connectivity and functional connectivity.

This study is an initial step in a series of future work that will focus on using rfMRI to analyze the changes found in lifelong high-end sensory motor activities (e.g. musicianship and multilingualism) and how these lifestyles contribute to building of cognitive brain reserve and other positive effects for healthy cognition in aging.

The COVID-19 crisis resulted in restricted access to Duke Hospital and to the scanners, which were unavailable for several months, thus limiting the overall number of participants. Future directions include a replication of the results across a larger data set of musicians and non-musician controls, exploration of how FNC plays a role in healthy aging and building cognitive brain reserve, and investigation of the functional activations and connectivity through fMRI and other direct comparisons of musicians and bi- or multilinguals. Lifelong, highly proficient musicians who have decades of active musicianship and who are also willing to volunteer to participate in a brain MRI study is a rare cohort. Studies with a larger number of participants of this level of professional musicianship will require significant recruitment time. Conducting studies that incorporate task fMRI, DTI, and other structural changes, including notions of cognitive flexibility are needed. Further, studies are needed to know how these brain findings transfer to behavioral and cognitive domains, and especially how they affect cognitive brain reserve. In this study, we attribute the difference in FNC to lifelong musicianship. The results reported here may potentially be related to a confounding variable that is associated with musicianship, for example, the number of hours of disciplined practice. Future studies are needed to dissociate such variables from musicianship. In addition, longitudinal studies are needed to further validate our findings.

Conclusions

In this exploratory study, we have analyzed rfMRI data from lifelong musicians. We hypothesized that musicians will have higher levels of FNC than controls between four FNs: the DMN, AUN, SMN, and the VSN. These networks are important in musicianship and each of these FNs were clearly identified in our data set of 16 participants (eight musicians and eight non-musicians). We examined how FNCs between FNs change across the lifespan of the participants and found that the FNCs generally increased in musicians and decreased in controls. Given the increase in white matter integrity found in these musicians in an earlier study (Andrews *et al.*, 2021), it is possible that this finding recapitulates the possible interaction between structural connectivity and functional connectivity discussed in Betzel *et al.* (2014), in which structural connectivity changes may affect changes in functional connectivity patterns across the life span. It should be noted that our results are based on correlation and not causation. Further investigations are needed to establish the direct causal effect of music on cognitive reserve. Results of this study are preliminary and need to be replicated with a larger number of participants.

Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by E.A., C.E., and A.M. Data analysis were performed by all authors. The first draft of the manuscript was written by C.E and E.A. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

This research was funded by Duke University and the U.S. Department of Education, LRC Grant CFDA 84.229A.

Acknowledgements

This research was funded by Duke University and the U.S. Department of Education, LRC Grant CFDA 84.229A.

Institutional Review Board

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Duke University Health System Institutional Review Board (protocol code Pro00014272).

Informed Consent

Informed consent was obtained from all participants involved in the study.

Data Availability

Data sharing not applicable to this article for ethical and privacy reasons.

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