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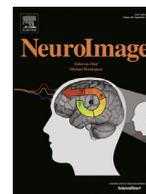
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The impact of early musical training on striatal functional connectivity

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ABSTRACT

Evidence from language, visual and sensorimotor learning suggests that training early in life is more effective. The present work explores the hypothesis that learning during sensitive periods involves distinct brain networks in addition to those involved when learning later in life. Expert pianists were tested who started their musical training early (<7 years of age; $n = 21$) or late ($n = 15$), but were matched for total lifetime practice. Motor timing expertise was assessed using a musical scale playing task. Brain activity at rest was measured using fMRI and compared with a control group of nonmusicians ($n = 17$). Functional connectivity from seeds in the striatum revealed a striatal-cortical-sensorimotor network that was observed only in the early-onset group. In this network, higher connectivity correlated with greater motor timing expertise, which resulted from early/late group differences in motor timing expertise. By contrast, networks that differentiated musicians and nonmusicians, namely a striatal-occipital-frontal-cerebellar network in which connectivity was higher in musicians, tended to not show differences between early and late musicians and not be correlated with motor timing expertise. These results parcel musical sensorimotor neuroplasticity into a set of musicianship-related networks and a distinct set of predominantly early-onset networks. The findings lend support to the possibility that we can learn skills more easily early in development because during sensitive periods we recruit distinct brain networks that are no longer implicated in learning later in life.

1. Introduction

The brain is shaped by experience throughout the lifespan, but remains most receptive early in development (Dahmen and King, 2007; Knudsen, 2004; Bischof, 2007; Penhune, 2011, 2020). These moments of heightened receptivity, referred to as 'sensitive periods', represent time windows when neural circuitry within a specific domain is particularly malleable and training can have lifelong effects. Just as early visual experience has life-long consequences by establishing the functional organization of primary visual cortex (e.g., Hensch, 2005; Hubel and Wiesel, 1962; Wiesel and Hubel, 1963), how does more complex early motor training impact the organization of large-scale functional systems?

Learning to play a musical instrument is a unique example of complex motor learning, as it requires integration across the full range of sensory, motor, affective and cognitive domains. While sustained long-term practice is paramount to mastery (Herholz and Zatorre, 2012;

Wan and Schlaug, 2010; Münte et al., 2002), training early in childhood confers a disproportionate and life-long advantage (Penhune, 2011, 2020; Merrett et al., 2013; but see also Wesseldijk et al., 2021). Early training likely facilitates behavioral benefits through heightened neural receptivity during childhood, as reflected in the observation of extensive changes across the cerebral cortex and cerebellum (Bailey et al., 2013; Watanabe et al., 2007; Baer et al., 2015, Meyer et al., 2011; Skoe and Kraus, 2013, Vaquero et al., 2016). In particular, the striatum has been linked to piano mastery (Granert et al., 2011) and general musical learning (Tanaka and Kirino, 2016; James et al., 2014), and striatal morphology is disproportionately affected by early training (Vaquero et al., 2016). One function the striatum performs in musical instrument learning may be the automatization of learned motor sequences (Lehéricy et al., 2005; Lanciego et al., 2012). In addition, the striatum has a broad range of connections with the cortex involved in cognitive, attentional and affective functions (Postuma and Dagher, 2006) that may complement motor automatization to support music learning (Zatorre et al., 2007; Herholz and Zatorre, 2012).

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Table 1

a: Demographic summary of the groups included in the study. Descriptive statistics are reported as mean (SD) unless otherwise indicated. b: Statistical comparisons of the groups.

a			
	early-onset pianists	late-onset pianists	nonmusician controls
N	21	15	17
male/female	9/12	9/6	10/7
age (years)	24.43 (3.96)	23.60 (3.62)	24.06 (4.39)
parents monthly income (<5k, 5–10k, >10k EUR)	9 / 7 / 3	7 / 8 / 0	–
lifetime accumulated practice (x 1000 h)	14.45 (9.39)	12.11 (7.87)	–
current weekly practice amount (hours)	14.16 (9.38)	15.21 (11.45)	–
weekly practice amount last year (hours)	20.30 (11.90)	18.67 (15.22)	–
age-of-onset of musical training (years)	5.27 (0.77)	8.33 (1.99)	–
number of years of musical training	19.15 (3.86)	15.27 (3.10)	–
b			
	early vs. late	musicians vs. nonmusicians	
male/female	Fisher exact test $p=.50$	Fisher exact test $p=.57$	
age	$t[31.8]=0.65, p=.52$	$t[27.7]=0.02, p=.98$	
parents monthly income	Mann-Whitney U test, $W = 153.5, p=.69$	–	
lifetime accumulated practice	$t[33.0]=0.81, p=.42$	–	
current weekly practice amount	$t[26.4]=0.29, p=.77$	–	
weekly practice amount last year	$t[25.5]=0.35, p=.732$	–	
age-of-onset of musical training	$t[17.1]=5.66, p<.001$	–	
number of years of musical training	$t[33.4]=3.34, p=.002$	–	

More broadly, the interaction between the striatum and cortex is a key locus of change as individuals transition into adulthood (Menon, 2013). Early in life, the striatum is more strongly connected with the cerebral cortex and this connectivity gradually decreases (Supekar et al., 2009; Fareri et al., 2015; Barber et al., 2019). This increased striatal connectivity in early development may play a critical role in entraining the less developed mechanisms of the cortex while they are still maturing (Pasupathy and Miller, 2005; Tricomi et al., 2009). Early training may thus benefit from increased striatal input, conferring an advantage for skill learning.

If corticostriatal interaction plays a role in early training, does early musical training result in life-long effects on these systems? Investigating the impact of prior musical training on brain organization in adulthood offers the potential for insight into the distinct systems involved in early versus late learning. We hypothesized that if specific corticostriatal networks may be malleable early in life, training presented during this early phase would lead to lasting differences in functional connectivity (FC) observable later in life. To investigate this, we recruited a sample of expert pianists and compared functional connectivity between those who started early in life (before the age of 7; a widely used cutoff in this field) and those who started later, but were matched for total training time (Steele et al., 2013; Penhune, 2011). Functional connectivity was explored across a range of striatal seeds since musical training involves a combination of sensorimotor, cognitive, reward and other processes (Zatorre et al., 2007; Jäncke, 2009; Herholz and Zatorre, 2012), each of which implicates different striatal subregions (Postuma and Dagher, 2006; Di Martino et al., 2008). To assess whether the early-training functional differences were attributable to behavioural expertise we correlated them with pianists' motor timing expertise at their instrument (van Vugt et al., 2014). To assess whether the early-training functional differences were attributable to musical training in general, we also compared the pianists with an age-matched nonmusician control group. By characterizing whether distinct striatal functional networks are related to early versus late musical training, these findings offer insight into how age-appropriate training programs may target functional systems at varying stages of development and plasticity.

2. Methods

All participants were self-reported right-handed, as confirmed through the Edinburgh questionnaire. All groups consisted of university students. The control group had no musical training other than compulsory music lessons received in primary and secondary school. Musicians were recruited from the Hannover University of Music, Drama and Media, and consisted of advanced master-class students and professional pianists (Vaquero et al., 2016). After discarding two participants due to MRI data artifacts and excessive motion, data from 36 expert pianists (21 early-onset; 15 late-onset) and 17 nonmusicians were included in the current analyses (Table 1). Although the present sample largely overlaps with that of Vaquero and colleagues, the samples differ slightly because different subjects were excluded. Participants received financial compensation for their participation in the study, which was approved by the Ethics Committee of the MHH (Medical School of Hannover).

The pianists were divided by the self-reported age of onset of musical training into an early-onset group (age of onset before 7 years, $n = 21$) and late-onset group ($n = 15$) and were matched for total lifetime practice time and other variables (Table 1). Prior literature used this age-7 cutoff and documented various behavioural and morphological brain differences in those who started early (Schlaug et al., 1995; Watanabe et al., 2007; Bailey and Penhune 2010; Steele et al., 2013; Penhune and de Villers-Sidani 2014; Bailey et al., 2014; Baer et al., 2015; Vaquero et al., 2016). Musical training variables (total lifetime practice in number of hours, weekly practice amount last year, current weekly practice time) were assessed using a self-report questionnaire. The pianists reported their amount of daily practice (in hours) for the following age segments of their life: 4–10, 11–15, 16–20, 21–25, 26–30, 31–35 years old. Based on this, and taking into account breaks in practice, the overall lifetime practice and weekly practice time for the current and last year were calculated. Although the difference in accumulated lifelong practice time between the early and late groups was not significantly different ($t[33.0]=0.81, p=.42$), we included this variable as a nuisance regressor in follow-up analyses that contrast early and late pianist groups.

2.1. Motor timing expertise

Motor timing expertise was assessed at the piano in the musician groups using a scale playing task previously shown to be a meaningful indicator of expertise (Jabusch et al., 2009; van Vugt et al., 2013, 2014). Pianists played on a Kawai MP9000 stage piano and were instructed to play C major scales over two octaves as regularly in time as possible, at mezzo-forte loudness and in legato style. Participants had to use the conventional fingering (i.e. 123,123,412,312,345 for ascending scales, where the numbers represent the fingers from 1=thumb to 5=little finger). Participants played alternating ascending and descending scales with the left or right hand. A metronome (120 beats per minute) indicated the desired tempo and participants had to play four notes within a beat (i.e. eight keystrokes per second), which constitutes a challenging motor task for expert pianists. Keystroke timings were collected through an M-Audio MIDI-to-USB converter and read using in-house software for offline processing. Participants were asked to play 15 ascending and 15 descending scales, i.e. a total of 30 scales. If the experimenter noticed errors during playing, a few more scales were recorded so that there would be 30 usable scales. A total of 30.98 scales (SD 1.64) were recorded per pianist.

To quantify motor timing expertise, we computed the ‘temporal unevenness’ of scale playing for each participant. For each correctly played scale, we calculated the standard deviation of the time interval between the onset of subsequent keystrokes (ms). The median of standard deviations was taken as the temporal unevenness score for scales played with each hand and scale-direction, resulting in four scores per participant (left/right hand; ascending/descending scales). Lower temporal unevenness indicates better motor performance. ANOVA was used to compare groups and assess generalised effect sizes (η^2).

2.2. MRI image acquisition

MRI data was acquired prior to the scale playing task using a 3 Tesla MRI scanner (Siemens Allegra Magnetom). Anatomical images were acquired at 1mm³ isotropic resolution using a magnetization-prepared, rapid-acquired gradient echo (MPRAGE) sequence (192 sagittal slices, TR = 16 ms, TE = 4.9 ms). Resting-state functional MRI (fMRI) data were acquired while participants were instructed to lie quietly with their eyes closed, to avoid any head motion during the scan, and to avoid mental focus. After each scan, participants were asked if they fell asleep and if so the scan was repeated. Blood-oxygen level dependent (BOLD) fMRI data was acquired using echo-planar imaging (EPI). We collected 178 volumes with 3 mm isotropic resolution (including 34 slices with a 0.75 mm slice gap, TE=30 ms, TR=2000 ms) yielding a total scan duration of approximately 6 min. This provided whole-brain coverage, except for the cerebellar tonsils in 40 of 53 participants.

2.3. MRI preprocessing

The anatomical and functional data were preprocessed using a combination of AFNI (Cox, 1996) and FSL5 (Smith et al., 2004) using Nipype pipelines (Gorgolewski et al., 2011) and the C-PAC interface (<https://fcp-indi.github.io/>) as well as a set of custom scripts. Anatomical images were registered to the MNI152 template at 1 mm resolution using nonlinear warping techniques implemented by the Advanced Normalisation Tools (ANTS, <https://stnava.github.io/ANTS/>). Functional preprocessing included: discarding four initial volumes to allow magnetization saturation; slice-timing correction; motion-correction; boundary-based co-registration of the average functional volume to individual anatomical space; nuisance regression using 5-component CompCor (Behzadi et al., 2007) (based on anatomically defined white matter and CSF masks) and motion regression from the Friston 24-parameter model (Friston et al., 1996); and band-pass filtering at 0.01–0.1 Hz.

2.4. Seed-based correlation analysis

Six seed regions within the striatum of each hemisphere were created based on locations identified in Di Martino et al. (2008) (Fig. 1): dorsal caudate (DC; MNI coordinates x,y,z = [±13,15,9]), ventral striatum (superior) (VSs; [±10,15,0]), ventral striatum/nucleus accumbens (inferior) (VSi; [±9,9,-8]), dorsal rostral putamen (DRP; [±25,8,6]), dorsal caudal putamen (DCP; [±28,1,3]), and ventral rostral putamen (VRP; [±20,12,-3]). Each seed region consisted of a spherical mask with a 3 mm radius. The mean of the preprocessed time series was computed for each individual, and then Pearson correlated with all voxels in the brain. Correlation coefficients were converted into Fisher z-values and smoothed using a 6 mm full width at half maximum (FWHM) Gaussian kernel.

We next contrasted the functional connectivity maps across groups. We created a design matrix with two independent variables: musician-ship (two levels: pianist and nonmusician) and training onset (early vs. late). The early/late column of the design matrix was coded -1 for late pianists, +1 for early pianists, and 0 for nonmusicians. Statistical maps were thresholded with cluster forming threshold $z = 2.5$ and then corrected for multiple comparisons using Gaussian Random Field theory (GRF) in FSL FLAME. The cluster significance level was set at $p = .05/6 = 0.008$ to correct for six independent tests. Although 12 seed regions were analyzed, bilateral homologues are highly correlated (see SI Figure S8). Therefore, following common practice in the field, we Bonferroni-corrected for six comparisons, or half the statistically independent tests. To obtain correlations with behavior, functional connectivity values were averaged within each significant cluster, resulting in one value per cluster per subject. We then calculated the correlations of these with motor timing expertise for each cluster separately.

3. Results

We assessed the impact of early musical training on striatal functional connectivity in a group of adult pianists who began their training either early (before the age of 7) or late in childhood (Table 1). Probing functional connectivity from a set of seed regions (Fig. 1) distributed throughout the striatum (Di Martino et al., 2008) resulted in connectivity maps similar to those documented previously in healthy adults (Fig. 2 and SI Fig. S2), broadly following an arc of functional specialization where ventral caudate seed regions are linked to reward, dorsal caudate and dorsocaudal putamen linked to cognitive, and caudal putamen most associated with motoric patterns of functional connectivity. The statistical maps for these and the following results are also available at <https://neurovault.org/collections/QOPMTKNP/>

We observed patterns of functional connectivity that were unique to early-onset musicians (Fig. 3). Comparison of early versus late-onset pianists revealed significantly higher functional connectivity between several striatal seeds (bilateral DC, VRP and right VSs) and regions through-

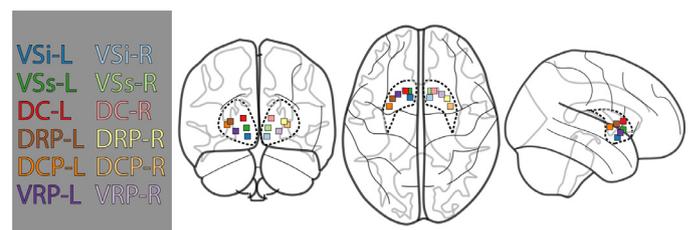


Fig. 1. Striatal seed regions used for whole-brain functional analysis. Six non-overlapping seed regions (3 mm radius) were generated based on the MNI coordinates described by Di Martino et al., 2008, and are illustrated here in coronal, axial, and sagittal views. VSi = ventral caudate/nucleus accumbens, VSs = ventral caudate, superior, DC = dorsal caudate, DCP = dorsocaudal putamen, DRP = dorsorostral putamen, VRP = ventrorostral putamen.

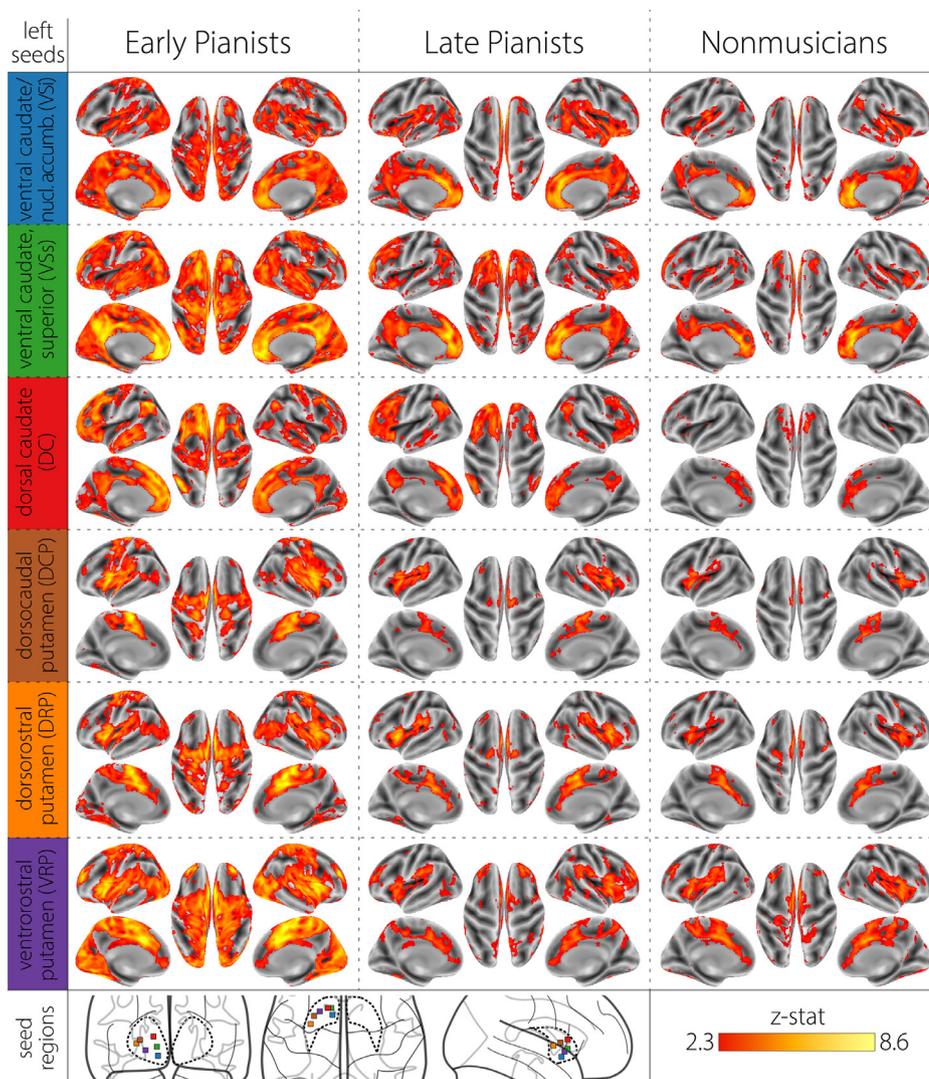


Fig. 2. Functional connectivity results from six striatal seed regions. Cortex that showed significant functional connectivity with the left hemisphere seed regions (rows) in early-onset pianists, late-onset pianists or nonmusicians (columns). Bottom inset: locations of the striatal seed regions. Note that analyses were performed in the volume but presented here on the cortical surface.

out sensorimotor cortex in the early-training group (Table 2). The cortical areas included primary sensorimotor areas. This cluster extended over the middle part of the central sulcus within the hand/wrist area of primary motor cortex, which was visually identified using the morphological feature of the ‘omega’ sign (Yousry et al., 1997). The cluster extended into the premotor and supplementary motor area (SMA). Post-hoc analyses of the significant clusters further demonstrated that functional connectivity within the early-onset musicians was significantly positive (all $t[30] > 6.13$, $p < .0001$, Cohen $d > 1.37$), whereas functional connectivity in the late-onset group did not significantly differ from zero (all $t[30] < 1.26$, $p > .23$). In addition, this pattern of connectivity was specific to the early-onset group, as revealed by the similarity observed in functional connectivity across the late-onset group and nonmusicians (all $t[30] < 2.39$, $p > .16$; Fig. 3). Although total lifetime practice did not significantly differ across early- and late-onset pianists, we nevertheless confirmed that early vs. late differences held when variance due to accumulated practice was regressed from the functional connectivity values in the clusters. We also investigated group differences in early pianists vs. combined late pianists and nonmusicians, which showed comparable results to the early vs. late comparison. This is accounted for by the similarity of functional connectivity maps in the late musician and nonmusician groups (see Fig. 2). Taken together, these findings suggest a distinct set of striatal connections forming networks that on a group level are seen only in those that commenced their training early in life.

To further assess whether the functional connectivity patterns identified above were specific to the onset of training or were a general result of any musical training, we compared functional connectivity between all pianists and nonmusicians. While several clusters were identified in the occipital and frontal cortex (Fig. 4), as well as cerebellar regions (SI Fig. S4) that significantly differed across the groups, none were in the sensorimotor regions identified in the early vs. late contrast. Further, these functional connectivity relationships did not generally differ between early- and late-onset pianists (see Table 2). The one exception was the functional connectivity between right VSs and the lingual gyrus, which was greater in early- compared to late-onset pianists. In sum, these results indicate that there are specific increases in corticostriatal functional connectivity related to musical training irrespective of when the training began. This musicianship-related network of corticostriatal functional connectivity did not overlap with the pattern of early/late differences.

To investigate whether patterns of functional connectivity that were unique to early-onset musicians were related to the behavioural gains observed in the early trained group, we measured motor timing expertise at the instrument. Early-onset pianists exhibited better performance (lower temporal unevenness, mean 10.14 ms, SD 1.53 ms), than late-onset pianists who began their training after the age of seven (mean 12.63 ms, SD 3.23 ms; $F[1,27] = 7.17$, $p = .01$, $\eta^2 = 0.16$), even though the groups were matched for total lifetime practice (Table 1). We found that

Table 2

Overview of significant clusters. Early>Late Table indicates seeds and clusters for which early-onset pianists show greater connectivity than late-onset pianists. Pianists>Nonmusicians Table indicates the pairs of seeds and clusters for which pianists showed greater connectivity than nonmusicians. Cluster P indicates the cluster p-value after Gaussian Random Field theory correction. Max-Z indicates the peak z value. X,Y, Z indicate MNI coordinates of the peak z value. *Early vs. late* indicates statistical comparison of the functional connectivity in these clusters between early and late musicians after regressing out any differences that could be explained by accumulated lifetime practice. Abbreviations: Cb=Cerebellum, IFG=Inferior Frontal Gyrus, S1=Primary sensory cortex, M1=Primary motor cortex, SMA=Supplementary Motor Area. For more detailed anatomical description of the clusters, see SI Tables S1 and S2.

Early > Late Pianists								
seed	lat.	# Voxels	Cluster P	max-Z	cluster designation	x	y	z
DC	L	246	0.000176	4.06	M1 (L)	-21	-18	75
DC	L	200	0.000911	4.21	M1 (R)	45	-9	66
VRP	L	1913	<0.0000001	4.52	Occip Pole, Intracalc Cort (L,R)	-3	-90	-3
VRP	L	1309	<0.0000001	4.64	S1, M1, SMA (L,R)	-3	-18	69
VSSs	R	664	0.000000018	4.23	S1, M1 (L,R)	45	-30	63
DC	R	1118	<0.0000001	4.35	M1 (R)	60	-6	48
VRP	R	228	0.00305	3.8	M1 (R)	39	-18	51

Pianists > Nonmusicians									
seed	lat.	# Voxels	Cluster P	max-Z	cluster designation	x	y	z	Early vs. late
VSSs	L	233	0.0074	4.05	Cb IV, V (L,R)	21	-42	-21	$t = 0.83$ $p=.41$
DC	L	500	0.000147	4.23	SFG, IFG	-18	66	9	$t = 0.33$ $p=.75$
DRP	L	271	0.000889	3.65	Lingual, Cingulate Gyrus (L)	-33	-45	-9	$t = 0.04$ $p=.97$
VSi	R	407	0.000111	3.96	Occipital lobe, fusiform gyrus (L)	-33	-84	-21	$t=-0.13$ $p=.90$
VSSs	R	460	0.000009	4.18	Lingual Gyrus (medial)	-6	-84	-15	$t=-2.73$ $p=.01$
DC	R	251	0.00355	4.33	Cb V, Temporal Occipital Fusiform Cortex (R)	42	-45	-18	$t=-1.20$ $p=.24$
DRP	R	181	0.00158	3.77	Inf/Middle Occip Gyrus, MTG (R)	45	-63	15	$t = 0.77$ $p=.45$

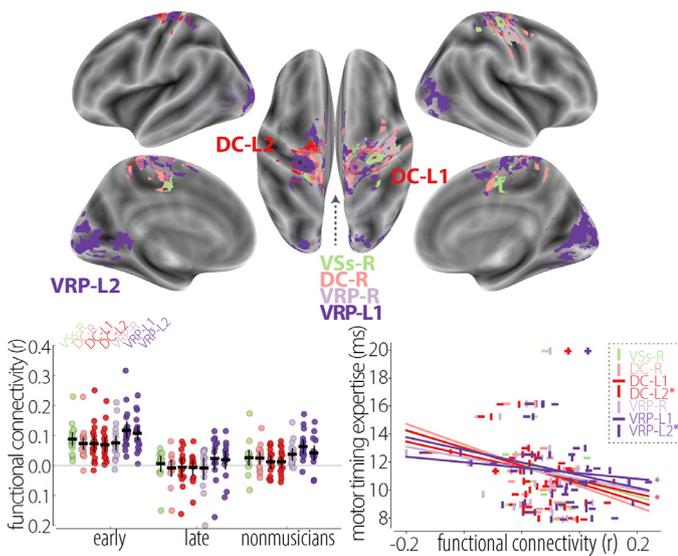


Fig. 3. Group differences in functional connectivity between early- and late-onset pianists. Early-onset pianists exhibited greater functional connectivity than late-onset pianists between the seed regions and a set of occipital and cortical sensorimotor areas, whereas functional connectivity to these areas was comparable between late-onset pianists and nonmusicians. The color of each patch indicates the seed region for which the area indicated greater functional connectivity. Barplot: functional connectivity across the seed regions (error bars indicate 2SE). Scatter plot indicates the correlation between functional connectivity and motor timing expertise (in ms; lower values correspond to greater expertise). Pianists who did not complete the scale playing task are omitted from the scatter plot. Analyses were performed in the volume but presented here on the cortical surface. VSi = ventral caudate/nucleus accumbens, VSs = ventral caudate, superior, DC = dorsal caudate, DCP = dorsocaudal putamen, DRP = dorsorostral putamen, VRP = ventrorostral putamen.

functional connectivity in the early>late clusters (Fig. 3) was generally correlated with motor timing expertise (all Spearman $r < -0.28$, $p < .07$), where greater functional connectivity was associated with greater motor timing expertise. The cluster in occipital cortex (associated with

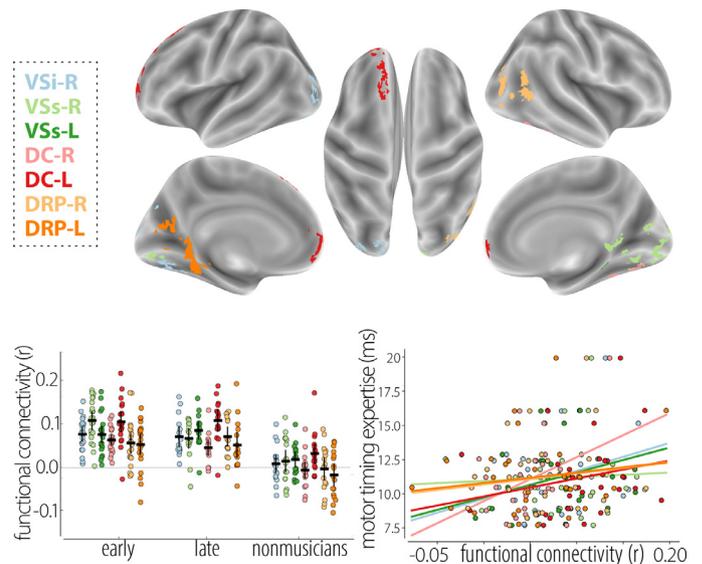


Fig. 4. Group differences in functional connectivity between pianists and nonmusicians. Pianists exhibited greater functional connectivity than nonmusicians between the seed regions and a distributed set of areas, but connectivity was not different between the early- and late-trained pianists. The color of each patch indicates the seed region for which the area indicated greater functional connectivity. Barplot: functional connectivity across the seed regions. Scatter plot indicates the correlation between functional connectivity and motor timing expertise (in ms; lower values correspond to greater expertise). Pianists who did not complete the scale playing task are omitted from the scatter plot. Analyses were performed in the volume but presented here on the cortical surface. VSi = ventral caudate/nucleus accumbens, VSs = ventral caudate, superior, DC = dorsal caudate, DCP = dorsocaudal putamen, DRP = dorsorostral putamen, VRP = ventrorostral putamen.

left VRP) was the only exception (Spearman $r=-0.15$, $p=.21$). Functional connectivity in the areas that differed between pianists and nonmusicians did not correlate with motor timing expertise (all Spearman $|r| < 0.24$ $p > .11$ except for a marginal correlation between left DC and a

Early > Late networks for various age cutoffs

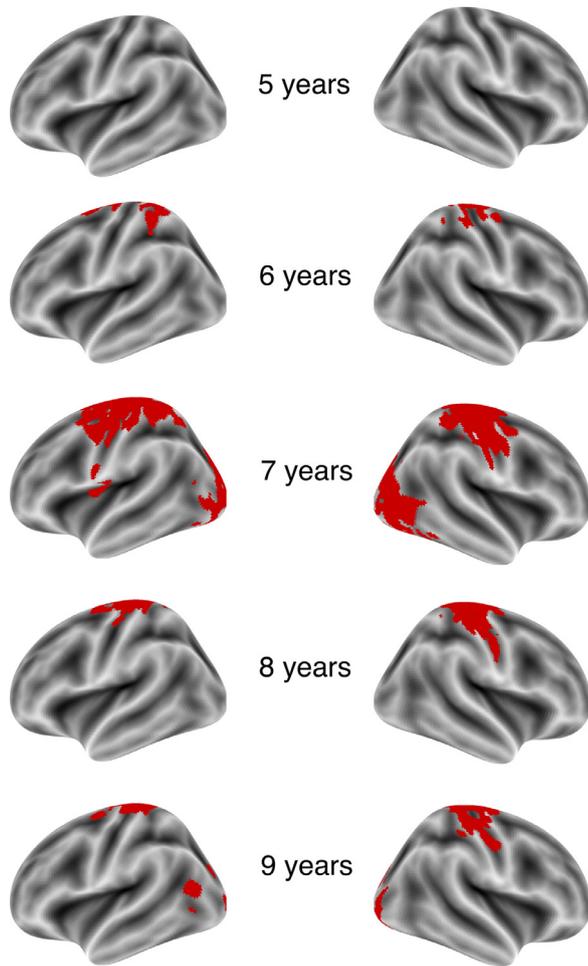


Fig. 5. Windowing analysis reveals similar findings when using other age cut-offs (5, 6, 7, 8, 9 years of age) while the cutoff age of seven yields the greatest differences between early and late onset pianists. The figure rows show the binarised union of all significant clusters for all seeds.

cluster in the frontal medial cortex, Spearman $r = 0.31$, $p = .05$) (Fig. 4). In sum, the patterns of functional connectivity that were unique to early-onset musicians correlated with motor timing expertise whereas the connectivity differences between pianists and nonmusicians did not.

In order to understand whether functional connectivity in the early-training network was more strongly related to onset of training (early/late) or motor timing expertise, we inserted these two variables as predictors into a multiple regression for each seed. We found that early/late onset was significant in all cases (all $t > 2.52$, $p < .02$) and motor timing expertise was no longer significant (all $|t| < 1.73$, $p > .10$). This suggests that the FC differences more strongly reflect early/late training than motor timing expertise. The observed correlation between functional connectivity and motor timing expertise results from the benefit that early training conferred on motor timing expertise.

The early and late onset groups were defined based on age of onset and were matched for age at the time of testing. As a result the groups differed in total number of years of musical practice (Table 1), but they did not differ according to total number of hours at the instrument. In the case of music playing, it is thought that not the number of years of practice but rather the amount of hours practiced, influences musical skill (Jabusch, 2009). We also controlled for participant age as well as volumetric differences and showed that these did not confound the results (see SI section ‘Controlling for volumetric differences’).

The present study divided participants into early and late starters using the cutoff of 7 years of age. Although this cutoff is widely used (Schlaug et al., 1995; Watanabe et al., 2007; Bailey and Penhune 2010, 2013; Steele et al., 2013; Bailey et al., 2014; Baer et al., 2015; Vaquero et al., 2016) the reason this precise age was chosen appears largely arbitrary. There is little empirical support for using age 7 specifically but observations suggest age effects broadly reach a plateau around that age (Bailey and Penhune, 2013). To investigate whether the effects observed here would be robust to the choice of age cutoff, the same analysis was repeated, splitting participants at the age of 5, 6, 8 or 9. In order to enable direct comparison between the results, the thresholded, cluster-corrected result maps for the different seeds were binarized and merged yielding a single mask for each age split (Fig. 5). These maps were also further combined across seeds into an overall union map. It was found that the map with the greatest spatial extent was from the analysis using age 7 as cutoff. The various age cutoffs identified largely the same network, as shown by the fact that the age 7 map covered 80.9% of the union of all analysis maps (Dice coefficient 0.89), but the other ages appeared less sensitive because they covered at most 35.1% of the combined results (Dice coefficient 0.52) (Fig. 5). This analysis suggests that although different age of onset cutoffs yield similar results, the group differences are most pronounced for the age of 7 used in the main analyses in the rest of this paper.

4. Discussion

The present study demonstrates that musical training has long-term effects on corticostriatal functional connectivity in adults who began musical training earlier, rather than later in childhood. Specifically, in pianists who began training earlier, functional connectivity was increased between sensorimotor cortical and ventral striatal regions. These patterns did not overlap with functional connectivity differences due to musical training. Early trained musicians also showed greater motor timing expertise (measured as precision in playing musical scales). We interpret these results in the context of the unique lifelong impact of training during sensitive periods, leading to altered corticostriatal interactions and enduring behavioral advantages.

Sensitive periods are windows during development where training produces larger effects than at other times, reflecting an interaction between neurocognitive maturation and experience (Penhune, 2011, 2020; Bengtsson et al., 2005; Trainor, 2005). In functional terms, training is thought to modify the energetic landscape of the brain so that certain connections become stable and subsequently occur spontaneously (Knudsen, 2004). We focus here on striatal connectivity because of its role in early neural development as well as its specific implication in musical expertise (Granert et al., 2011; James et al., 2014; Vaquero et al., 2016). While sensitive periods have been extensively studied in visual (Hensch, 2005; Fagiolini and Hensch, 2000; Morishita and Hensch, 2008; Hubel and Wiesel, 1962; Wiesel and Hubel, 1963; Benoit et al., 2015) and auditory systems (Kral, 2013; Kral et al., 2005), higher cognitive skills such as language learning have also been a topic of investigation (Kuhl, 2010; Patkowski, 1980; Oyama, 1976; Jackson, 2000). In the case of language, early learning proceeds largely without explicit instruction, whereas later in life learning proceeds through explicit rules and problem-solving strategies (Bley-Vroman, 2009; DeKeyser, 2000). Although the idea of developmentally-specific learning strategies has not been described in the musical domain, it is possible that early and late training rely on different mechanisms, which are supported by distinct neural systems. Similar to the language domain, learning a new musical skill early or late may have differential effects on the functional organization of the brain. Although the functional brain impact of early music learning has not been directly studied, prior studies have documented that early music training was associated with enhanced sensorimotor timing and learning (Jäncke et al., 1997; Watanabe et al., 2007; Bailey et al., 2013; Baer et al., 2015), auditory perception (Meyer et al., 2011; Skoe and Kraus, 2013) and mu-

sical scale playing (Vaquero et al., 2016). Brain structure differences in early trained musicians that likely underpin these behavioural benefits include: white matter fiber tract organization (Bengtsson et al., 2005), intrasulcal length of the precentral gyrus (Amunts et al., 1997), size of anterior corpus callosum (Schlaug et al., 1995), anatomical connectivity in corpus callosum (Steele et al., 2013) and gray matter in premotor cortex (Bailey et al., 2013), striatum (Vaquero et al., 2016) and cerebellar lobule VI (Baer et al., 2015). Taken together, these lines of evidence demonstrate that musical training during sensitive periods yields greater learning and this is reflected in differences in brain structure in a variety of learning domains.

Our results suggest a long-term impact of early childhood piano training on functional connectivity between ventral striatal and sensorimotor cortical regions. This network included primary sensorimotor cortices, and, for seeds in the more ventral-rostral portions of the striatum this network extended to the premotor and supplementary motor area (SMA) (Fig. 3). These areas are part of a network implicated in musical behaviors and structurally affected by musical training. In previous work, primary motor cortex surface area was shown to be larger in musicians who began training earlier (Amunts et al., 1997). More specifically, cortical representation of the fingers was shown to be enlarged in musicians commensurate with the age at which they had begun training (Elbert et al., 1995). Premotor areas are implicated in mapping sounds to action (Bangert et al., 2006; Lahav et al., 2005, 2007), and have been found to have greater cortical surface area in early-, compared to late-trained musicians (Bailey et al., 2013). Likewise, a prior study using our cohort found the striatum to be structurally different according to the early/late onset of musical training (Vaquero et al., 2016). Specifically, the right putamen demonstrated smaller gray matter volume in the early-onset group. Our current findings, however, showed an increase in functional connectivity between the putamen and cortical regions, raising the question of how these seemingly contradictory findings relate with one another. It is important to note that the functional connectivity findings here were not driven by structural differences which we ruled out with a separate analysis. Prior work investigating learning-induced plasticity in structural and functional connectivity measures found that the long-term modulation of functional connectivity preceded structural changes (Taubert et al., 2011). It remains unclear how the increase in functional connectivity relates to the decrease in putamen volume. While prior work has noted a similar mismatch in the direction of changes between these two measures (Baliki et al., 2012), structural and functional changes provide two perspectives on early/late onset related differences, the connection between which remains to be understood. Taken in the context of this prior work documenting volumetric differences in striatum in early vs. late trained pianists, our results demonstrate that differences in the brain induced by early musical training extend beyond the local impact on regional morphology to include the interaction between these systems, which may be key to the improved ability for musical learning early in life through directly targeting the motor systems involved in music perception and production.

Early learning confers life-long behavioral advantages for core skills of musicianship, such as enhanced rhythm and sensorimotor synchronization (Watanabe et al., 2007; Bailey et al., 2013; Baer et al., 2015), finger tapping (Jäncke et al., 1997) and musical timing (Vaquero et al., 2016) (but see also Hosoda and Furuya, 2016). This behavioural advantage of early training was observed in the present study as well in terms of motor timing expertise, and the link between motor timing expertise and functional connectivity was attributable to early/late group differences. Nevertheless the brain areas in question have been previously linked with music-related functions such as rhythm perception and production. For example, functional connectivity between the striatum and premotor cortical regions as well as SMA has been shown to be modulated by the presence of a beat in a rhythmic sequence (Grahn and Rowe, 2009). Of specific relevance to the present findings, SMA is furthermore implicated in bimanual coordination (Serrien et al., 2002), and its activity during passive listening predicts later musical learning

(Wollman et al., 2018). Considering our results in the context of this previous work, striatal-cortical connectivity appears to be part of the network that enables skilled musical performance especially when this skill is acquired early in life.

While the benefits of early training for musicianship are substantial, musical training, regardless of when it is initiated, has profound effects on brain structure and function. Prior work has found differences related to musical training in gray matter volume within auditory, motor and visuospatial cortical regions (Gaser and Schlaug, 2003; Groussard et al., 2014; Han et al., 2009; Gärtner et al., 2013) and increased connectivity between sensory and motor areas during listening or mute musical playing (Bangert et al., 2006; Lahav et al., 2007). In addition, long-term musical training affects functional connectivity between sensory and motor regions (Luo et al., 2012; Fauvel et al., 2014; Klein et al., 2016), which is impacted by the amount of practice (Palomar-García et al., 2016). In line with this literature, the present study also showed corticostriatal functional connectivity differences between pianists and nonmusicians (cf. Fig. 3). In pianists functional connectivity with frontal regions was greater than in non-musicians, including the inferior frontal gyrus (IFG), an area that previous work implicating this region in musical expectancy (Osnes et al., 2012; Seger et al., 2013) and musical syntax processing (Tillmann et al., 2006). Various portions of the putamen (right VSi, DC and DRP) showed increased connectivity with occipital areas in musicians. There is mounting evidence that links occipital areas to musical training: musicians showed greater interhemispheric asymmetry in gray matter in the occipital pole (Luders et al., 2004), and increased connectivity with primary auditory and motor cortex (Luo et al., 2012). We also observed increased striatal functional connectivity with the lingual and fusiform gyri in musicians compared to nonmusicians. This is in line with prior findings of greater gray matter volume in the lingual gyrus in musicians (Vaquero et al., 2016; Sato et al., 2015) and enhanced functional connectivity with auditory areas in musicians (Luo et al., 2012). The lingual and fusiform gyri are visual associative fields of the ventral visuo-fugal pathway, which is implicated in higher order pattern recognition (Mesulam, 1998). The fusiform gyrus is implicated in recognition of faces (Haxby et al., 1991; Kanwisher et al., 1997), but also more generally in pattern recognition across a variety of disciplines such as car experts, ornithologists, radiologists and chess players (Gauthier et al., 2000; Harley et al., 2009; Bilalić et al., 2010). In musicians, the fusiform gyrus and V3 are implicated in reading musical notation (Wong and Gauthier, 2010; Nakada et al., 1998; Muayqil et al., 2015). Together with the present finding this supports the notion that the strength of striatal-occipital functional connectivity may be related to expertise in processing musical notation. Post hoc analysis further demonstrated that these functional connectivity relationships did not generally differ between early- and late-onset pianists (Table 2). The one exception was the functional connectivity between right VSs and the lingual gyrus, which was greater in early- compared to late-onset pianists. While this latter finding is tentative, it may indicate that early training confers greater impact on functional connectivity associated with visuospatial processing or visual memory, perhaps implicated in musical score reading. In sum, musical training affects the brain regardless of the age at which it occurs, but these changes in brain connectivity were found to be independent of the early-training induced changes and of motor timing expertise.

While our results within both the late-onset pianist and nonmusician groups were consistent with prior observations of corticostriatal functional connectivity (Di Martino et al., 2008), the early-onset group alone deviated from these patterns, which notably included more caudal portions of striatum than traditionally involved in motoric functions (Fig. 3). Prior research advanced the caudal putamen as most associated with motoric patterns of functional connectivity. Our results revealed a more complex picture where the striatal region most related with motoric expertise was in fact the dorsal caudate. Thus, our exploratory approach suggests the subparts of the striatum other than those classically assigned to motor function may contribute to early musical learning.

According to another model of corticostriatal interaction based on tract-tracing studies in the macaque monkey, connectivity patterns between the striatum and cerebral cortex are characterized by a progression of parallel loops extending along the rostral–caudal axis (Alexander et al., 1986; Haber, 2003). Studies in the human brain using functional connectivity have confirmed these patterns, revealing connectivity between regions of ventral striatum with higher-order cognitive and affective cortical regions (Di Martino et al., 2008), rather than the inclusion of functional connectivity with sensorimotor systems found here in the early-training group. It is intriguing to consider that the present results may reflect a sensitive period in development when the spectrum of corticostriatal connectivity is amenable to global alterations based on experience. Recent methods have been introduced to characterize global corticostriatal organizational gradients (Marquand et al., 2017), and such approaches may help provide further insight into the large-scale impact of early-training in future work.

The current study measured brain organization in adulthood, decades after the training we claim to have impacted on their current functional organization. While resting-state functional connectivity networks are generally consistent and reliable across individuals (Damoiseaux et al., 2006; Zuo et al., 2010), they can also be modulated by training (Taubert et al., 2011; Lewis et al., 2009). Relatively short-term motor practice results in changes to resting-state functional connectivity immediately following learning (Vahdat et al., 2011; Della-Maggiore et al., 2017; Albert et al., 2009; Bernardi et al., 2018; van Vugt et al., 2020). Persistent changes in resting state connectivity such as studied here have been documented for example in athletes (Di et al., 2012), meditators (Taylor et al., 2013), and musicians (Luo et al., 2012; Klein et al., 2016). A limitation of the current study is that we only investigated musicians, and therefore it remains unclear whether the same pattern of findings observed here holds for other forms of sensorimotor training as well. While future longitudinal studies are needed to adjudicate the causal influence of early musical training on long-term functional organization of corticostriatal systems, our findings support the notion that in addition to the type and amount of training, the time during development when this training occurs may impact its long-term effect on brain organization.

The present study revealed that early musical training is associated with an increase in functional connectivity between cortical and striatal regions as measured in adulthood, which is not observed in those who began training later in childhood. While further work is required to assess the direct impact of early training on functional networks, this line of research holds promise for improving pedagogy. For example, musical training may be tailored to the age of the student, with younger students receiving a kind of training that most effectively drives the early plasticity, and later students receiving training building on cognitive systems specific to their developmental level.

Declaration of Competing Interest

None.

Credit authorship contribution statement

F.T. van Vugt: Conceptualization, Data curation, Methodology, Formal analysis, Software, Writing – original draft, Writing – review & editing. **K. Hartmann:** Conceptualization, Data curation, Writing – review & editing. **E. Altenmüller:** Conceptualization, Writing – review & editing, Supervision, Project administration. **B. Mohammadi:** Data curation, resources. **D.S. Margulies:** Conceptualization, Writing – review & editing, Supervision.

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Data availability statement

The anatomical and functional data were preprocessed using a combination of AFNI (Cox, 1996) and FSL5 (Smith et al., 2004) using Nipype pipelines (Gorgolewski et al., 2011) and the C-PAC interface (<https://fcp-indi.github.io/>) as well as a set of custom Python and R scripts.

Version numbers of the various packages we used are listed here below: nibabel==2.5.0 nilearn==0.5.2 nipype==0.4.2 nipype==1.0.4 pandas==0.24.1 pydicom==1.0.2

The statistical maps for all contrasts reported in the manuscript are available at: <https://neurovault.org/collections/QOPMTKNP/>

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2021.118251](https://doi.org/10.1016/j.neuroimage.2021.118251).

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