Lifelong musical activity is associated with multi-domain cognitive and brain benefits in older adults

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1 Abstract

Regular musical activity as a highly-stimulating lifestyle activity is proposed to be protective against age-related cognitive decline and Alzheimer's disease (AD). This study investigated associations between lifelong regular musical instrument playing, late-life cognitive abilities and brain morphology in older adults. We show that musical activity over the life course is associated with better global cognition, working memory, executive functions, language, and visuospatial abilities accounting for reserve proxies. Playing music is not significantly associated with gray matter volume in regions most affected by aging and AD. Selectively in the musically active participants, multi-domain cognitive abilities were enhanced with preserved gray matter volume in frontal and temporal regions. Our correlational findings suggest that playing a musical instrument may improve the recruitment of existing brain resources to facilitate late-life cognitive capacities. We propose that engaging in regular musical activity could serve as a low-threshold multimodal enrichment strategy that may promote cognitive resilience in advanced age.

Keywords: cognitive reserve, resilience, prevention, brain plasticity, instrument playing

2 Introduction

Healthy lifestyle activities are proposed to enhance brain and cognitive resilience in older adults [1] through multiple neuroprotective pathways [2-4] and may thereby offer protection against age-related neurodegenerative diseases, such as Alzheimer's disease (AD). Among others, regular musical activity, such as playing an instrument, has been associated with reduced risk of developing dementia [5,6]. To advance targeted intervention strategies, it is important to delineate cognitive benefits and underlying brain mechanisms associated with musical activity in advanced age.

Musical activity is suggested to share communalities with the concept of environmental enrichment [7,8], shown to promote far-reaching neurobiological and behavioral benefits in animal models [9]. Playing a musical instrument entails complex skills involving the simultaneous perception and integration of motor, sensory, cognitive, emotional, and social stimulations, thought to facilitate beneficial brain plasticity [10]. Consistently, there is evidence indicating that playing music could preserve higher-order cognitive abilities in older adults [11,12]. In this population, benefits of regular musical activity have been shown to transfer to multiple cognitive domains that typically decline with higher age, including executive functions, attention, language, visuospatial as well as memory abilities [13-17]. Together these findings imply that complex multimodal stimulation, as inherent to playing music, might help retain cognitive capacities in late life.

Comparatively little is, however, known about the neurobiological underpinnings of regular musical activity in older adults [18]. Studies that have investigated brain correlates of playing music in young and middle-aged cohorts suggest that this activity leads to plasticity, as reflected in measurable volume increases in distributed brain areas [19,20]. Those areas comprise multisensory frontal, partial, and temporal regions [21-23], which are strongly affected by healthy and pathological aging [24-26]. Regularly participating in musical activity may also be protective for the hippocampus. In young musicians compared to controls, musical activity is associated with enhanced volume and functions of the hippocampus [27-29]. In older adults, there appears to be a volume increase in frontal and temporal areas associated with playing music [30]. Such benefits in brain resources may contribute to better late-life cognitive abilities associated with this lifestyle activity.

Overall, the existing findings propose that regular musical activity may protect brain and cognitive health via multiple pathways. There might be a boost in functional brain capacities and/or an increase in structural brain resources, both of which may help counteract neuropathological burden in

advanced age [31]. To shed light onto these mechanisms, this cross-sectional study investigated potential cognitive and brain benefits of playing music during the entire life in the older population. Taking into account reserve proxies of educational attainment, crystallized intelligence, socioeconomic status (SES), and physical activity, we hypothesized that lifelong regular musical activity is associated with better late-life cognitive abilities in multiple domains as well as larger gray matter volume (GMV), particularly in regions affected by healthy and pathological aging. We further investigated, whether playing an instrument has a positive influence on the association between regional brain structure and cognitive performance in older adults, proposed to convey cognitive resilience in advanced age.

3 MATERIAL AND METHODS

3.1 Overall design of the DELCODE study

The data used in this study were obtained from the DZNE-Longitudinal Cognitive Impairment and Dementia cohort. The detailed study protocol can be found in a previous report [32]. In brief, the DELCODE cohort was set up to recruit 1000 participants at baseline with five groups of participants. Specifically, these groups are healthy controls (HC), first-degree relatives of AD patients (family history, FH) as well as participants with subjective cognitive decline (SCD), mild cognitive impairment (MCI), and mild AD dementia. At baseline assessment, all participants received extensive clinical, neuropsychological, and behavioral assessments. To minimize site-effects and ensure high data quality, assessment protocols were standardized across sites using Standard Operating Procedures (SOP). Post-scanning MRI image quality assessments were conducted by the DZNE Magdeburg. The DELCODE study protocol agreed with ethical principles for human experimentation in accordance with the Declaration of Helsinki. At each participating study sites, the protocol was approved by the local ethical committees. All participants gave their written informed consent. DELCODE was registered at the German Clinical Trials Register (DRKS00007966; April 5, 2015).

3.2 Participants

In the present study, cognitively healthy participants (HC, FH, and SCD) were included and merged across the three groups to increase the final sample size. Recruitment procedures including inclusion and exclusion criteria are described in detail elsewhere [32]. In brief, all participants were aged ≥ 60 years, German speaking, able to provide informed consent and had a study partner serving as an informant. Normal cognitive function was defined as a test performance within -1.5 standard deviations of age-, sex- and education-adjusted norms on all subtests of the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) test battery [49]. Exclusion criteria for HC, FH, and SCD were comprised of medical conditions including current or past major medical, neurological, or psychiatric disorders. Presence of SCD was defined by subjectively reported decline in cognitive functioning with concerns [50]. Diagnostic criteria for MCI and mild AD dementia are provided in Jessen et al. (2018).

The DELCODE baseline dataset (total: n = 1079) was used to select a subset of participants into the present study as follows (see Figure 1): At the time of our analysis, data from 943 participants with a structural cranial magnetic resonance imaging (MRI) assessment at baseline were available. Of

these participants, cognitively healthy participants were selected (i.e., HC, SCD, FH, total: *n* = 678). Afterwards, participants who reported regular musical activity across the life span (i.e., group of interest) and participants with no musical activity during life (i.e., control group) were identified (total: *n* = 429; for methodological details see below). Finally, we matched the control group and included only participants with complete datasets regarding variables of interest, resulting in a final sample of *n* = 140 (for methodological details see below).

3.3 Measurements

3.3.1 Measurement of musical activity

Musical activity across lifespan was assessed using the Lifetime of Experiences Questionnaire [47], adapted for the German population [51]. Details on the LEQ and the coding scheme used to assess lifelong regular musical activity are provided in the supplementary material. In brief, the self-reported questionnaire measures educational, occupational, and leisure activities across three life periods (young adulthood: 13 – 30 years, mid-life: 30 – 65 years, and late-life: 65 years onwards). One self-reported lifestyle activity inquired by the LEQ was the frequency of playing a musical instrument and this information was used to operationalize musical activity across the lifespan. Similar to a previous study [33], we constructed a variable that was comprised of two groups: (1) The musical activity group (group of interest) included those participants that were musically active in all life periods and reported regular musical activity (2 times per month or more) in at least one life period. (2) The no musical activity or control group included participants that reported to never have played a musical instrument in any of the life periods.

3.3.2 Measures of cognitive abilities

Cognitive functioning was assessed using latent factors over five cognitive domains, namely (1) learning and memory, (2) working memory, (3) executive functions and mental processing speed, (4) language, and (5) visuospatial abilities, created by summarizing cognitive tests from the extensive neuropsychological test battery in the overall DELCODE cohort as described previously [52]. In brief, Wolfsgruber et al. (2020) used confirmatory factor analyses (CFA) to extract the factor structure using data from the extensive neuropsychological test battery applied during baseline assessment. Additionally, a global cognitive performance score was calculated by taking the mean of the five cognitive scores [52]. For the present analysis, we used performance measures for global cognition and

the five cognitive domain scores. Each cognitive score was z-transformed using the selected DELCODE neuroimaging sample including HC, FH, and SCD participants.

3.3.3 MRI acquisition and processing

MRI data were acquired using Siemens MRI scanners (Siemens, Erlangen, Germany), including three TIM Trio systems, four Verio systems, one Skyra system, and one Prisma system. The extensive MRI protocol of the DELCODE study is described elsewhere [32]. For the present analysis, we used T1-weighted images (i.e., 3D GRAPPA PAT 2, 1 mm^3 isotropic, 256 × 256 px, 192 slices, sagittal, ~ 5min, TR 2500 ms, TE 4.33 ms, TI 110 ms, FA 7°) and T2-weighted images (i.e., 0.5 × 0.5 × 1.5 mm^3, 384 × 384 px, 64 slices, orthogonal to hippocampal long axis, ~12 min, TR 3500 ms, TE 353 ms, optimized for volumetric assessment of the medial temporal lobe). All scans underwent quality assessment provided by the DZNE imaging network (iNET, Magdeburg).

Regional GMV analysis was conducted in pre-selected regions-of-interest (ROI), robustly affected by healthy and pathological aging due to AD [24-26]. Based on these findings, we chose two regions, that is, the frontal lobe and the hippocampus. For each of these ROIs, we used regional volume measures provided in the DELCODE database, as described previously [53]. In brief, structural MRI images were segmented in native space using an automated cortical parcellation pipeline [54] implemented in FreeSurfer (version 6.0, http://surfer.nmr.mgh.harvard.edu/) and an advanced segmentation tool [55] to derive ROI-based GMV. To enhance reliability, image segmentation was based on T1-weighted and high-resolution T2-weighted images. Left and right hippocampal volume were summed for a measure of the overall hippocampal volume. Frontal volume was calculated as the sum over left and right frontal ROI of the Desikan atlas following the procedure described elsewhere [56]. In addition, cortical GMV was evaluated as a global measure of brain integrity. Regional GMV measures were adjusted for total intracranial volume (TIV), as estimated using FreeSurfer [57], using a ratio.

We also assessed GMV at the voxel level. Structural MRI images were segmented to extract GM, WM, and CSF tissues using the unified segmentation algorithm in CAT12 (version 12.6, http://dbm.neuro.uni-jena.de/vbm) with default parameters. Warping to the Montreal Neurological Institute (MNI) template space was performed using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) with default parameters and registration to existing templates [58]. Total intracranial volume (TIV) was computed as the sum of volumes of GM, WM, and CSF using the SPM “Estimate TIV and global tissue volumes” routine. Voxel-based statistical analyses were

198 performed on the warped and modulated GMV maps, which were smoothed by a three-dimensional
199 Gaussian kernel with full width at half maximum of 8 mm^3.

200 #### *3.3.4 Additional measures*

201 Age, sex, education, intelligence, SES, self-reported participation in physical activity and
202 diagnostic group were considered as potential confounders. Educational attainment was measured in
203 years of education. Crystallized intelligence was estimated using the Multiple-Choice Vocabulary
204 Intelligence Test (MWT, min. score: 0, max. score: 37), with scores proportional to crystallized
205 intelligence [59].

206 Participation in long-term physical activity was estimated using respective information from the
207 LEQ. A mean score was calculated over responses on the frequency of physical activity over two or
208 three life stages (i.e., < 65 years and ≥ 65 years, respectively). In addition, current physical activity
209 was assessed through the Physical Activity Scale for the Elderly PASE, [60]. The PASE includes leisure,
210 household and occupational activities assessed over the previous week. Based on frequency,
211 duration, and intensity of these activities, a total score is calculated with higher scores indicating
212 greater levels of physical activity. Long-term physical activity was significantly correlated with current
213 physical activity in the matched sample (n = 140, r = 0.35, p < 0.001), supporting the validity of the
214 measure. Long-term physical activity was used as a covariate in statistical analyses, since the
215 measure was available from all participants.

216 The SES was calculated for each participant using information on occupational activity
217 assessed by the LEQ. Details are provided in the supplementary material. In brief, details on
218 occupational activities of each respondent were obtained using 10 five-year intervals across middle- to
219 late-life adulthood (i.e., 30 to 79 years of age). The information was used to calculate the international
220 socio-economic index of occupational information (ISEI, min. score: 16, max. score: 90) [61] using a
221 fully-automated procedure. The ISEI scores were averaged across time intervals to obtain one mean
222 SES measure per participant. The SES measure was positively and significantly associated with the
223 LEQ sum scores measuring educational as well as occupational activity for young (n = 140, r = 0.54, p
224 < 0.001) and middle (n = 140, r = 0.69, p < 0.001) adulthood, indicating the validity of the estimated
225 ISEI scores.

226 ### 3.4 Statistical analyses

Statistical analyses were conducted using *R* (version 3.5.1.) and Statistical Parametric Mapping (SPM, version 12, Wellcome Trust Centre for Neuroimaging, London, UK). Figures were generated using the package *ggplot2* [62]. Before conducting statistical models, statistical assumptions were assessed visually using diagnostic plots.

3.4.1 Sample characteristics and matching procedure

Participants with lifelong musical activities and controls with no musical activity were matched using a one-to-one matching procedure taking into account age, sex, diagnostic group, education, SES, intelligence, and physical activity. Details are provided in the supplementary material. The procedure was carried out using propensity score matching with the *R* package *MatchIt* (version 4.1.0.) [63]. Observations were matched based on the nearest-neighbor method, as a simple and effective procedure for selecting well-matched groups [64]. Musical activity groups were compared in baseline demographic, behavioral, neuropsychological, and neuroimaging variables. Independent Student's *t*-tests were used for all continuous variable and chi-squared (χ^2) tests were applied for all categorical variables.

3.4.2 ROI-based analyses

To assess our main hypotheses, multiple linear regression models were used. In these statistical analyses, an alpha value of 0.05 was considered statistically significant. In addition, correction for multiple comparisons was performed using a false discovery rate (FDR)-adjusted p-value threshold (alpha) of 0.05 [65]. Uncorrected p-values were reported, when results survived FDR correction, this is specifically indicated.

Firstly, the association of musical activity (modelled as a main effect) with global cognition followed by the domain-specific abilities were assessed. Multiple linear regression models were performed including with musical activity (binary group variable) as an independent variable and each cognitive measure (z-transformed composite score) as a dependent variable, respectively. Next, the association between musical activity and brain structure was examined using similar multiple linear regressions. Models included musical activity (binary group) as independent variable and ROI-based GMV (frontal region and hippocampal region, both TIV adjusted) as dependent variable along with scanner site as covariate (dummy coded). Selected relationships were visualized to facilitate the interpretation of findings using box plots of unadjusted data.

Secondly, we assessed the moderating effect of musical activity on the relationship between ROI-based GMV and cognitive abilities. To do this, musical activity, ROI-based GMV (frontal region and hippocampal region, both mean-centered), the interaction term (musical activity × GMV), and scanner site as covariate (dummy coded) were entered into regression models with each cognitive factor score as dependent variable. To specify the directionality of the interactions, simple slope analyses were conducted [66,67]. Interaction effects were visualized using unadjusted data as follows: General and domain-specific cognitive scores (z-transformed) were graphed as a function of musical activity and ROI-based GMV, respectively. In addition, we examined whether or not the respective relationships differed significantly from zero within each group.

3.4.3 Voxel-based analysis

To further evaluate the spatial distribution of musical activity-associated effects on brain structure at the voxel level, exploratory voxel-wise general linear models (GLM) were conducted in SPM12. For the present purpose, voxel-wise results were presented at $p < 0.001$ uncorrected at peak level in combination with the estimated expected voxels per cluster (k) as automatically calculated by SPM.

Firstly, a GLM was computed with musical activity as independent variable and the modulated, warped, and smoothed GMV maps as dependent variable. Secondly, a moderating effect of musical activity was evaluated at the voxel level. This GLM included musical activity, the respective cognitive measure (z-transformed composite score), and the interaction term (musical activity × cognitive measure) as independent variables with GMV maps as dependent variable. The later analysis was carried out for global cognition and all cognitive domains. For reasons of simplicity, results of this analysis were displayed for one cognitive domain, selected by the strongest interaction effect in the ROI-based analysis.

All voxel-based analyses were adjusted for TIV as well as scanner site (dummy coded) and restricted to cerebral GM using an explicit binary GM mask derived from the present sample (i.e., average GM maps thresholded at a level of > 0.3, excluding cerebellum and brain stem). Cluster peaks are specified by their anatomical site, labelled using the Hammersmith atlas [68] provided by the CAT12 toolbox. Finally, mean values were extracted in significant clusters for each participant from the warped, modulated, and non-smoothed GMV images using the Marsbar toolbox (release: 0.44; http://marsbar.sourceforge.net/) [69], to provide complementary visualizations of the associations.

4 Results

4.1 Sample characteristics

This study included a total sample of 140 older participants (aged ≥ 60 years) selected from the ongoing, multi-center, observational DELCODE cohorts [32]. The present sample comprised 70 individuals with lifelong regular musical activity and 70 controls with no musical activity over the life course (see Figure 1). The two groups (musical activity, no musical activity) were comparable in age, sex, distribution of diagnostic groups as well as reserve proxies of higher education, crystallized intelligence, SES, and participation in both long-term and current physical activity (all *p's* > 0.05, Table 1). Slight group differences in frontal and total GMV (unadjusted raw values) were found, with larger volumes in the older participants with lifelong musical activity compared to controls.

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Figure 1

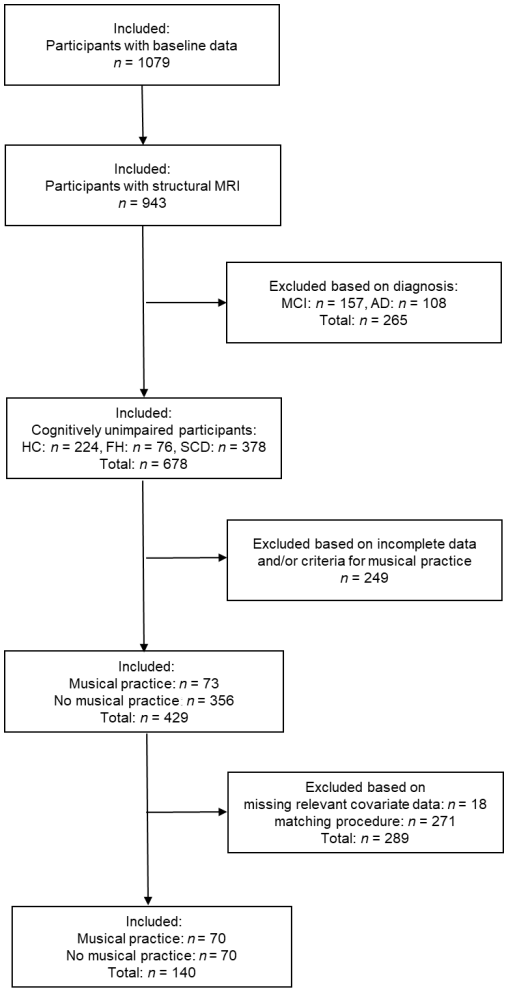

Figure 1: Participant selection flowchart. The graph displays the selection procedure from the DELCODE database. ***Key:*** HC, healthy controls; FH, family history of AD; AD, Alzheimer's disease; MCI, mild cognitive impairment; Magnetic resonance imaging (MRI).

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Table 1

Table 1: Descriptive characteristics of the matched sample (*n* = 140)

	Musical activity	No musical activity	P value
Number (n)	70	70	-
Age (years)	68.23 (6.62)	69.01 (5.44)	0.445
Gender female/male (n)	31/39	35/35	0.498
Education (years)	16.20 (2.71)	15.96 (2.74)	0.598
Diagnostic group HC/ FH/SCD (n)	19/7/44	24/6/40	0.654
SES [a]	66.27 (16.32)	65.21 (16.04)	0.699
Crystalized intelligence [b]	33.31 (2.14)	33.04 (2.22)	0.463
Physical activity, long-term [c]	4.25 (0.78)	4.32 (0.71)	0.611
Physical activity, current [d]	33.86 (11.80), *n* = 66	32.45 (12.85), *n* = 69	0.507
Total hippocampal GMV (sum, ml)	6.26 (0.71)	6.21 (0.66)	0.692
Total frontal GMV (ml)	138.86 (12.44)	134.69 (11.88)	0.044*
Total cortical GMV (ml)	453.83 (37.56)	441.69 (37.13)	0.049*

Descriptive data are given if applicable as mean and standard deviation (in parenthesis). The actual sample size is provided, if different from sample size specified in first row. *P* values correspond to independent *t*-tests for unequal variance with participant group as independent variable. Chi-square statistic was used to compare the distribution of categorical variables.
***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.
Key: HC, healthy control participants; FH, participants with family history of AD; GMV, gray matter volume; SCD, participants with subjective cognitive decline; SES, socioeconomic status.
[a] International socio-economic index (ISEI); [b] Multiple-Choice Vocabulary Intelligence Test (MWT); [c] Lifetime of Experiences Questionnaire (LEQ); [d] Physical Activity Scale for the Elderly (PASE).

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4.2 Musical activity and cognition

Applying multiple linear regression models to assess the associations between musical activity and cognitive performance, we found significant group differences for global cognition, working memory, executive function, language and visuospatial abilities (Table 2). Performance in these cognitive domains was significantly better in the older participants with lifelong regular musical activity compared to controls. In contrast, no association of musical activity was found with the domain of learning and memory ($p = 0.209$).

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313 ***Table 2***

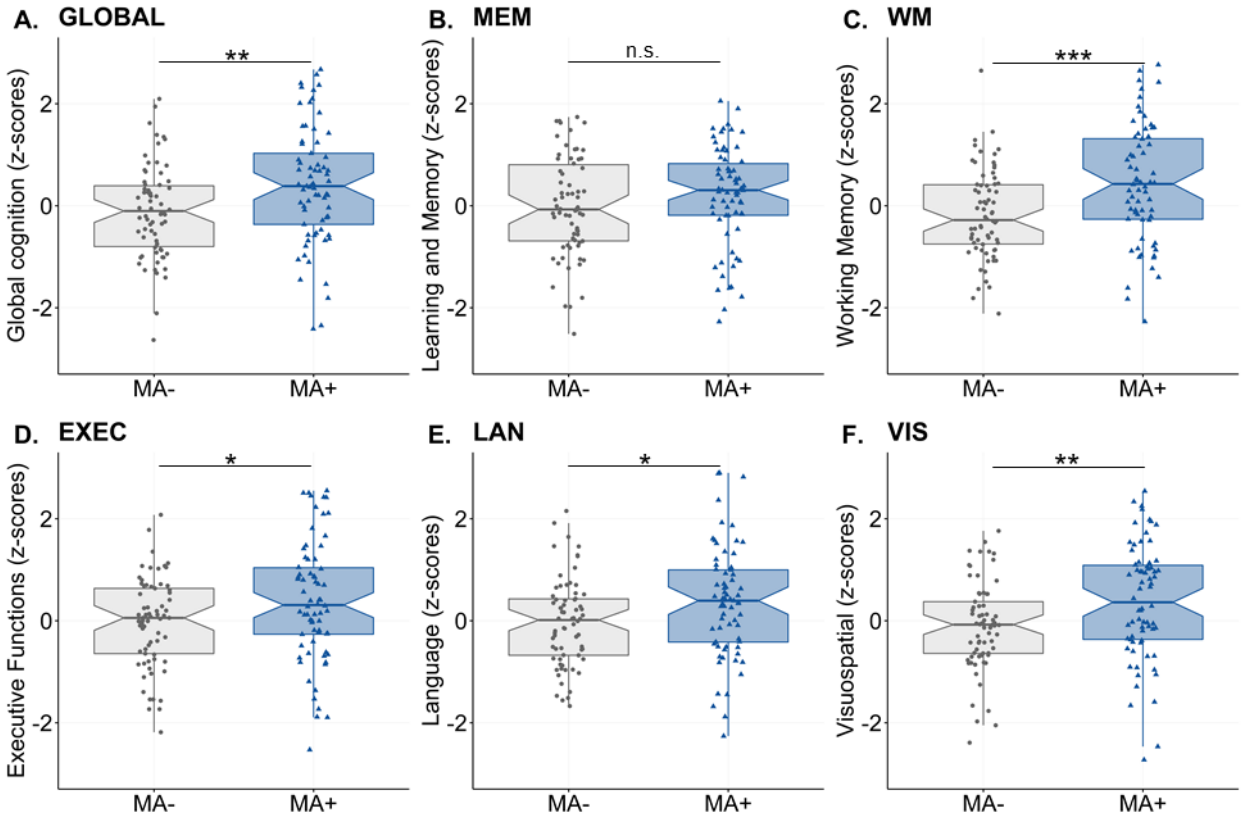
Table 2: Results of linear regression analyses between musical activity and cognition

	Dependent variable	Independent variable	B	SE B	Beta	P value	Total R^2 (adj.)
1	Global cognition	Musical Activity	0.540	0.178	0.250	0.003**†	0.062 (0.056)
2	Learning and Memory	Musical Activity	0.209	0.165	0.107	0.209	0.011 (0.004)
3	Working Memory	Musical Activity	0.669	0.178	0.304	< 0.001***†	0.092 (0.086)
4	Executive Functions	Musical Activity	0.465	0.180	0.214	0.011*†	0.046 (0.039)
5	Language	Musical Activity	0.443	0.170	0.216	0.010*†	0.047 (0.040)
6	Visuospatial	Musical Activity	0.522	0.176	0.245	0.003**†	0.060 (0.053)

Musical activity was included as binary predictor, dummy coded with musical activity = 1, no musical activity = 0.
***p < 0.001, **p < 0.01, *p < 0.05.
† p < 0.05 false discovery rate (FDR)-adjusted for statistical tests performed across cognitive domains.
Key: B, unstandardized coefficient; SE, standard error; Beta, standardized coefficient; R^2, explained variance

314 ==========

315 ***Figure 2***



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317 **Figure 2: Main effect of lifelong musical activity on cognitive abilities.** Significant group differences were
318 found for global cognition (A, GLOBAL, working memory (C, WM), executive function (D, EXEC), language (E,
319 LAN) and visuospatial abilities (F, VIS). These multi-domain cognitive abilities were enhanced for participants with
320 lifelong musical activity (MA+, blue) compared to controls (no musical activity across lifespan, MA-, gray). The
321 association was not significant for the learning and memory composite (B, MEM). Boxplots display unadjusted
322 data with individual data points. The "notch" shows the median with 95% confidence intervals and interquartile
323 range with lower (25th) and upper percentiles (75th). Significance levels (uncorrected): ***p < 0.001, **p < 0.01, *p
324 < 0.05. ***Key:*** MA+, musical activity; MA-, no musical activity.

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4.3 Musical activity and brain structure in regions-of-interest

Results for the associations between musical activity and GMV (TIV-adjusted values) in the selected ROIs are shown in Table 3. There were no significant differences between participants with lifelong musical practice compared to controls in frontal and hippocampal volume (all *p's* > 0.5). Also, the groups did not differ significantly in total cortical GMV ($p = 0.722$).

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Table 3

Table 3: Results of linear regression analyses between musical activity and GMV in regions-of-interest

	Dependent variable	Independent variable	B	SE B	Beta	P value	Total R^2 (adj.)
1	Frontal GMV	Musical Activity	-0.046	0.204	-0.020	0.822	0.120 (0.052)
1	Hpc GMV	Musical Activity	-0.007	0.012	-0.052	0.551	0.102 (0.032)
3	Cortical GMV	Musical Activity	-0.303	0.850	-0.031	0.722	0.132 (0.065)

Models adjusted for scanner site.
Musical activity was included as binary predictor, dummy coded with musical activity = 1, no musical activity = 0.
Regional GMV was adjusted by total intracranial volume (TIV).
***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.
† $p < 0.05$ false discovery rate (FDR)-adjusted for statistical tests performed across ROIs.
***Key*:** B, unstandardized coefficient; Hpc, Hippocampus; SE, standard error; Beta, standardized coefficient; R^2, explained variance; GMV, gray matter volume

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4.4 Moderations of musical activity in regions-of-interest

Moderation analyses were applied to assess the influence of musical activity on the associations between late-life regional GMV and cognitive performance (Table 4 and 5). Frontal GMV was positively associated with global cognition and domain-specific cognitive abilities (all *p's* ≤ 0.001, data not shown). Importantly though, significant interactions were observed between musical activity and frontal GMV for global cognition, working memory, and language abilities (all *p's* < 0.05; Table 4). Visualization of these relationships (Figure 3) indicated that these cognitive abilities were selectively enhanced in participates with musical activity and preserved GMV in the frontal regions (i.e., above the 90% percentile of the GMV distribution in AD patients). No similar effect was detected for the learning and memory domain. Hippocampal GMV was also positively associated with global cognition and domain-specific cognitive abilities (all *p's* < 0.01, data not shown). There were, however, no significant interactions between musical activity and hippocampal volume in the multi-domain cognitive abilities (all *p's* > 0.1, Table 5 and supplementary Figure 4).

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348 ***Table 4***

Table 4: Results of the interaction analyses between musical activity and frontal GMV

	Dependent variable	Independent variable	B	SE B	Beta	P value	Total R^2 (adj.)
1	Global cognition	Music Activity × Frontal GMV	0.318	0.139	0.261	0.024*†	0.332 (0.269)
2	Learning and Memory	Music Activity × Frontal GMV	0.102	0.132	0.092	0.441	0.263 (0.193)
3	Working Memory	Music Activity × Frontal GMV	0.432	0.141	0.348	0.003**†	0.335 (0.273)
4	Executive Functions	Music Activity × Frontal GMV	0.278	0.145	0.228	0.058	0.273 (0.204)
5	Language	Music Activity × Frontal GMV	0.316	0.133	0.274	0.019*†	0.320 (0.256)
6	Visuospatial	Music Activity × Frontal GMV	0.227	0.145	0.189	0.119	0.251 (0.180)

Models adjusted for scanner site.
Musical activity was included as binary predictor, dummy coded with musical activity = 1, no musical activity = 0.
Frontal GMV was adjusted for total intracranial volume and mean centered.
***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.
† $p < 0.05$ false discovery rate (FDR)-adjusted for statistical tests performed across cognitive domains.
Key: B, unstandardized coefficient; SE, standard error; Beta, standardized coefficient; R^2, explained variance

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350 ***Table 5***

Table 5: Results of the interaction analyses between musical activity and hippocampal GMV

	Dependent variable	Independent variable	B	SE B	Beta	P value	Total R^2 (adj.)
1	Global cognition	Music Activity × Hpc GMV	2.248	2.515	0.118	0.373	0.330 (0.266)
2	Learning and Memory	Music Activity × Hpc GMV	-0.727	2.350	-0.042	0.757	0.284 (0.216)
3	Working Memory	Music Activity × Hpc GMV	4.109	2.620	0.211	0.119	0.299 (0.233)
4	Executive Functions	Music Activity × Hpc GMV	2.268	2.640	0.118	0.392	0.268 (0.199)
5	Language	Music Activity × Hpc GMV	2.782	2.435	0.154	0.255	0.300 (0.234)
6	Visuospatial	Music Activity × Hpc GMV	0.897	2.547	0.047	0.725	0.290 (0.223)

Models adjusted for scanner site.
Musical activity was included as binary predictor, dummy coded with musical activity = 1, no musical activity = 0.
Hippocampal GMV was adjusted for total intracranial volume and mean centered.
***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.
† $p < 0.05$ false discovery rate (FDR)-adjusted for statistical tests performed across cognitive domains.
Key: B, unstandardized coefficient; Hpc, hippocampus; SE, standard error; Beta, standardized coefficient; R^2, explained variance

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Figure 3

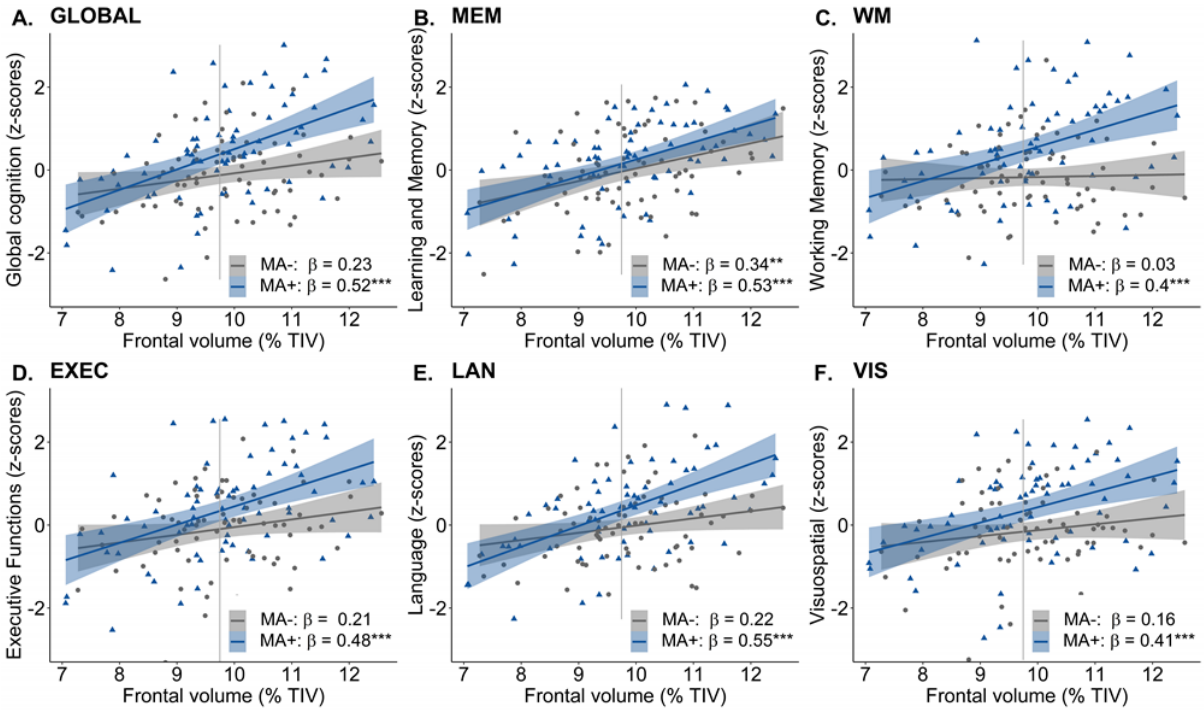

Figure 3: Moderation effect of lifelong musical activity in the frontal region. A significant moderation effect of musical activity was observed for global cognition (A, GLOBAL), working memory (C, WM), and language abilities (E, LAN), such that larger frontal volume (above the 90th percentile of the frontal volume distribution in AD patients) was associated with better global in participants with lifelong musical activity (MA+, blue) compared to controls (MA-, gray). This interaction was not significant for learning and memory (B, MEM), executive functions (D, EXEC), and visuospatial abilities (F, VIS). Individual data points (dots and triangles), linear trends (solid lines), 95% confidence intervals (shaded areas), and standardized regression coefficients (β) within each group are provided. Gray vertical lines display the 90th percentile of the frontal GMV distribution in AD patients of the DELCODE study. Significance levels (uncorrected): ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. ***Key:*** GMV, gray matter volume; MA+, musical activity; MA-, no musical activity; TIV, total intracranial volume.

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4.5 Voxel-based analysis

Results of the exploratory analyses at the voxel level are presented in Table 6 and Figure 4. There was a subtle positive association between lifelong regular musical activity and GMV within a smaller cluster in the left postcentral gyrus ($p < 0.001$ uncorrected). No other significant clusters were found. The interaction analysis corroborated a significant moderation of musical activity on the association between working memory and regional GMV ($p < 0.001$ uncorrected) in frontal (lateral and medial), inferior temporal, and precentral regions. Results of the moderation analyses across all

cognitive measures were essentially similar, with some variations in the number of significant clusters (supplementary Figure 6). No significant interaction effect was found for the domain of learning and memory at the voxel level.

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Table 6

Table 6: Results of analyses between musical activity and GMV at the voxel level

Model / contrast	No. cluster	Label	Hemisphere	Cluster		Peak of cluster			
				p	size	Z value	MNI coordinates (x y z)		
Main effect [a]									
Positive	1	Postcentral gyrus	left	0.176	239	3.66	-57	-6	26
Interaction effect [b]									
	1	Precentral gyrus	left	0.019	646	4.83	-28	-10	48
	2	Precentral gyrus	left	0.123	251	4.46	-38	-8	52
	3	Inferior middle temporal gyrus	right	0.048	437	4.42	51	-12	-42
	4	Inferior frontal gyrus	right/ lateral	0.171	194	3.70	40	33	12
	5	Superior frontal gyrus	right/ medial	0.273	122	3.47	6	36	-12

Models adjusted for scanner site and TIV.
Musical activity was included as binary predictor, dummy coded with musical activity = 1, no musical activity = 0.
[a] Results from the main effect model with musical activity and GMV ($p < 0.001$ uncorrected, expected voxels per cluster $k = 139$).
[b] Results from the interaction effect model with musical activity, working memory, and GMV ($p < 0.001$ uncorrected, expected voxels per cluster $k = 110$).
Cluster peaks are specified by their anatomical site, labelled using the Hammersmith atlas provided by the CAT12 toolbox.
Key: GMV, gray matter volume; MNI x y z [mm], coordinates MNI space in millimeters; TIV, total intracranial volume

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Figure 5

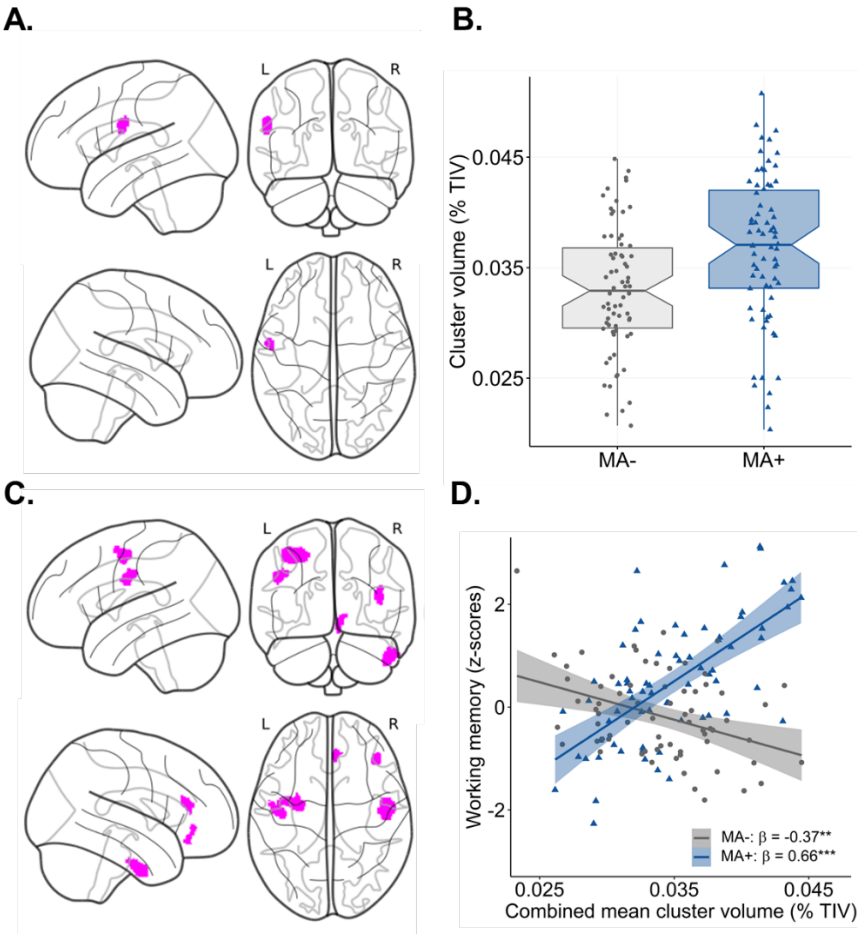

Figure 5: Associations between lifelong musical activity and regional volume distribution. A-B. Results of the main effect analysis. Statistical map (A) shows significant clusters ($p < 0.001$ uncorrected, color-coded in magenta) with larger GMV in participants with musical activity compared to controls. The corresponding graph (B) displays the association using mean GMV values extracted from the corresponding cluster in the postcentral gyrus. The box plot displays the median with 95% confidence intervals, interquartile range with lower (25th) and upper percentiles (75th), and individual data points. **C-D. Results of the interaction analysis.** The statistical map (C) displays clusters ($p < 0.001$ uncorrected, color-coded in magenta) with a significant moderation effect of musical activity. The corresponding scatter plot (D) shows the association using mean values extracted from the GMV maps in the combined cluster. Larger GMV in the combined cluster was associated with better working memory ability selectively in the musically active participants (MA+, blue) compared to controls (MA-, gray). Individual data points, linear trends (solid lines), 95% confidence intervals (shaded areas), and standardized regression coefficients (β) within each musical activity group are provided. The statistical maps are depicted on a glass brain. Significance levels (uncorrected): ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. ***Key:*** MA+, musical activity; MA-, no musical activity; GMV, gray matter volume; TIV, total intracranial volume.

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5 Discussion

5.1 Summary

The current study examined late-life cognitive abilities, brain morphology, and their interplay in cognitively healthy older adults as a function of regularly playing a musical instrument over the life course. Participants with a self-reported history of lifelong musical activity were compared to matched controls without musical activity across the lifespan. Results of this study highlight that regularly playing a musical instrument is associated with global and multi-domain cognitive benefits in older adults, with no significant benefit in gray matter structure in regions affected by aging and AD. In the musically active participants, cognitive abilities were enhanced with preserved regional GMV for some cognitive domains, pointing towards a facilitated recruitment of existing brain resources in this group. Overall, our findings may imply that a history of regular musical activity could promote cognitive and brain benefits in older adults and thereby strengthen resilience against cognitive decline.

5.2 Musical activity and cognition

We demonstrate that participants, who reported a lifelong regular engagement in musical activity, outperformed matched controls in cognitive performance. More precisely, superior cognitive abilities were found in global cognition and multiple cognitive domains including working memory, executive functions, language and visuospatial abilities in the musically active older people, with the largest effect size seen for working memory. These findings directly support and expand previous studies, showing that playing a musical instrument may preserve higher-order cognitive skills that typically decline in older adults [14,15,33,34]. By contrast, we did not identify benefits of musical activity on learning and memory, although these must be perceived as essential cognitive skill involved in playing music. In older adults, some studies report that regular musical activity is associated with better episodic memory [13,14,33], while others do not [8,15,16]. It might, however, be argued that specific hippocampus-related processes are enhanced by musical activity, such as long-term musical memory or navigation in acoustic space [27,35], but cannot be captured by the memory composite used in the current study. While sensitive experimental and neuroimaging markers are needed to gain insights into presumed memory benefits, current findings appear to confirm that regular musical activity may particularly favor late-life cognitive abilities involving the frontal lobe.

5.3 Musical activity and brain structure

Our data demonstrate that playing music during life was not significantly associated with larger GMV in age-sensitive brain regions. Specifically, we did not detect volumetric differences between musically active people and controls in frontal or hippocampal regions. The voxel-based analysis confirmed this observation. A slight volume increase was found in somatosensory areas of the musically active group, presumably reflecting brain plasticity in response to tactile stimulations induced by playing a instrument [21,22]. However, we failed to identify respective GMV modulations in higher-order brain regions. Earlier studies have shown positive associations between musical activity and brain volume in fontal, temporal, and parietal regions mainly in younger cohorts [21,22,27], with limited indication in older adults [30]. Similar to previous studies [15,16,33], we accounted for several reserve proxies that may help maintain late-life brain structure [3,36]. Given this effort, it seems plausible to assume that there is little benefit of regular musical activity on structural brain resources in older age. Alternatively, subtle effects could be unnoticed due to increased variability in GMV through differential brain aging and/or brain pathology [37].

5.4 Moderations of musical activity

Importantly though, our current results revealed that lifelong regular musical activity could act as a protective factor in the associations between late-life brain resources and cognitive performance. We found an interaction between playing music and GMV, such that performance in some cognitive domains was enhanced with preserved frontal volume selectively in the musically active participants. This specific moderation effect was significant for global cognition, language, as well as working memory and extended to inferior temporal as well as motor-sensory regions at the voxel level. In other words, although gray matter structure was not substantially associated with musical activity, it facilitated late-life cognitive performance in synergy with playing music. This may reflect a more efficient use of an overall younger brain age, as previously reported in amateur musicians compared to controls [38]. Our observation further parallels existing findings [29]. In their study, a larger hippocampal volume was associated with better general cognitive abilities in younger musicians, but not in non-musicians, implying that musically active people may be able to use existing brain resources more efficiently [29]. The current findings essentially indicate that this functional advantage of playing music is detectable in older adults, where it is linked to distributed brain regions and multiple cognitive domains. Frontal and temporal brain regions, in particular, are part of wide-spread brain networks shown to support cognitive reserve processes [36,39-42]. It therefore appears that playing music over the life course

could facilitate the recruitment of structural brain resources, as a key benefit to support late-life cognitive functioning.

5.5 Synopsis

Taken together, the present study adds considerable insight to the picture that musical activity over the life course, even at a moderate frequency, could act as protective factor in late life stages. Given that playing a musical instrument requires the simultaneous integration of intense multimodal motor, sensory, cognitive, emotional, and social sensations, this lifestyle activity may induce lasting functional plasticity in higher-order neural networks supporting multi-domain cognitive functions [43,44]. Even passive listening to music was previously shown to modulate functional connectivity in distributed brain networks [45], a mechanism suggested to convey therapeutic benefits of music-based interventions [7]. Enhanced functional connectivity in higher-order brain networks is an essential mechanism shown to be protective against neuropathological burden in older adults [39,41]. In light of our findings, it may be proposed that musical activity could act as a resilience factor through functional brain resources, which need to be examined in future studies.

Nevertheless, the observed health benefits associated with lifelong regular musical activity could be encouraged by a general engagement in advantageous lifestyles. Similar to previous studies [33], participants with regular musical activity during the life course were characterized by a high reserve profile including higher education, SES, intelligence, and more frequent physical activity. Notably though, we observed better cognitive abilities in the musically active group with these factors accounted for, suggesting an added benefit of musical activity on late-life brain and cognitive functions beyond known reserve proxies. Overall, our results propose that playing a musical instrument could serve as a low-threshold multimodal enrichment strategy that may help preserve cognitive and brain health. Targeted intervention studies are required to evaluate the impact of playing music on cognitive performance and underlying brain mechanisms in older people [46].

5.6 Strengths and limitations

Our study has several strengths and limitations. We assembled data from the longitudinal observational DELCODE cohort to assess a well-characterized sample of cognitively unimpaired older adults with measures of demographics, cognition, lifestyle behaviour, and brain structure. This detailed phenotyping provided new evidence on potential health benefits of regular musical activity in older

adults. This study identified older people with a history of musical activity over three life stages and statistical analyses were based on multi-domain cognitive abilities and morphological brain measures all measured in the same participants.

Limitations of our cohort-based approach include the assessment of musical activity. While we obtained the frequency of musical activity using the LEQ [47], more detailed information on musical instrument type, age of acquisition, and intensity would be desirable given that these features may differentially impact brain plasticity and cognitive skills [14,48]. Furthermore, the present cross-sectional study design does not permit causal interpretations of the investigated associations. It might be possible that certain factors that were not accounted for, facilitate playing an instrument over the life course. Such factors may include genetic predispositions or advantageous early-life exposures, which could play a role in the observed relationships, warranting further investigations. Finally, potential benefits of musical activity call for a longitudinal study design, to evaluate if musically active older people are indeed more protected against cognitive decline, which will have important implications on public health strategies.

5.7 Conclusion

Results of the present study are promising and suggest that lifelong regular musical activity, as an accessible and multimodal leisure activity, could help mitigating age-related cognitive decline through benefits in functional brain resources. Further research is needed to assess detailed information about the nature of playing music and functional brain mechanisms associated with a history of regular musical activity over the life course. Given that world populations are aging and that age-related diseases pose healthcare challenges of utmost importance, interventional studies examining the protective effects of musical activity on the brain and cognitive functioning in older adults are greatly needed.

6 AVAILABILITY STATEMENTS

6.1 Data availability

The data that support findings of the present study are available on reasonable request.

6.2 Code availability

For this study, existing data analysis packages for statistical analyses were used. Scripts for the use of these packages are available online from the authors on reasonable request.

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8 Declarations

8.1 Ethics approval and consent to participate

The DELCODE study protocol was approved by the ethical committees of the medical faculties of participating sites. All participants gave written informed consent prior to study inclusion.

8.2 Availability of data and materials

The data that support findings of this study are available on reasonable request.

8.3 Disclosures

O. Peters received fees for consultation from Abbvie, Biogen, Eisai, Griffols, MSD Roche, and Schwabe. J. Priller received fees for consultation, lectures, and patents from Neurimmune, Axon, Desitin, and Epomedics. J. Wiltfang is an advisory board member of Abbott, Biogen, Boehringer Ingelheim, Immunogenetics, Lilly, MSD Sharp & Dohme, and Roche Pharma and received honoraria for lectures from Actelion, Amgen, Beeijing Yibai Science and Technology Ltd., Janssen Cilag, Med Update GmbH, Pfizer, Roche Pharma and holds the following patents: PCT/EP 2011 001724 and PCT/EP 2015 052945. J. Wiltfang is supported by an Ilidio Pinho professorship, iBiMED (UIDB/04501/2020) at the University of Aveiro, Portugal. E. Duzel received fees for consultation from Roche, Biogen, RoxHealth and holds shares in neotiv. F. Jessen received fees for consultation from Eli Lilly, Novartis, Roche, BioGene, MSD, Piramal, Janssen, and Lundbeck. The remaining authors report no disclosures relevant to the manuscript.

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8.5 Authors' contributions

Conceptualization and design of the current study: A.B., T.K., A.H., K.F., S.R., M.Wa., G.K., M.Wi.; Overall design and implementation of the DELCODE study: O.P., S.D.F., J.P., S.A., A.S., K.F., I.F., A.S., N.R., S.W., L.K., J.W., C.B., F.M., C.N., L.D., R.Y., K.B., D.J., R.P., B.R., S.T., I.K., C.L., M.M., J.D.H., P.D., M.E., K.S., E.D., F.J., S.R., M.Wa.; methodology/statistical analysis: A.B., A.Z., M.G., M.W.; interpretation of data: A.B., A.Z., T.K., A.H., K.F., S.W., S.R., M.Wa., G.K., M.Wi.; drafting and/or revision of manuscript and approval of the final version: : A.B., A.Z., T.K., M.G., A.H., K.F., O.P.,

566 S.D.F., J.P., S.A., A.S., K.F., I.F., A.S., N.R., S.W., L.K., J.W., C.B., F.M., C.N., L.D., R.Y., K.B., D.J.,

567 R.P., B.R., S.T., I.K., C.L., M.M., J.D.H., P.D., M.E., K.S., E.D., F.J., S.R., M.Wa., G.K., M.Wi.

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