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# Music training is neuroprotective for verbal cognition in focal epilepsy

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Focal epilepsy is a unilateral brain network disorder, providing an ideal neuropathological model with which to study the effects of focal neural disruption on a range of cognitive processes. While language and memory functions have been extensively investigated in focal epilepsy, music cognition has received less attention, particularly in patients with music training or expertise. This represents a critical gap in the literature. A better understanding of the effects of epilepsy on music cognition may provide greater insight into the mechanisms behind disease- and training-related neuroplasticity, which may have implications for clinical practice. In this cross-sectional study, we comprehensively profiled music and non-music cognition in 107 participants; musicians with focal epilepsy ($n = 35$), non-musicians with focal epilepsy ($n = 39$), and healthy control musicians and non-musicians ($n = 33$). Parametric group comparisons revealed a specific impairment in verbal cognition in non-musicians with epilepsy but not musicians with epilepsy, compared to healthy musicians and non-musicians ($P = 0.029$). This suggests a possible neuroprotective effect of music training against the cognitive sequelae of focal epilepsy, and implicates potential training-related cognitive transfer that may be underpinned by enhancement of auditory processes primarily supported by temporo-frontal networks. Furthermore, our results showed that musicians with an earlier age of onset of music training performed better on a composite score of melodic learning and memory compared to non-musicians ($P = 0.037$), while late-onset musicians did not differ from non-musicians. For most composite scores of music cognition, although no significant group differences were observed, a similar trend was apparent. We discuss these key findings in the context of a proposed model of three interacting dimensions (disease status, music expertise, and cognitive domain), and their implications for clinical practice, music education, and music neuroscience research.

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**Abbreviation:** TLE = temporal lobe epilepsy

## Introduction

Focal epilepsy is a common neurological condition associated with deficits in executive functioning (working memory and attention), memory, visuo-spatial abilities, psychomotor speed, language, and general intellect (Laurent and Arzimanoglou, 2006; Hermann *et al.*, 2007; Kaaden and Helmstaedter, 2009; Helmstaedter, 2013). Neuroimaging research has proposed diverse cognitive profiles within relatively homogeneous focal epilepsy syndromes (Dabbs *et al.*, 2009). For instance, while language-related difficulties have been extensively studied

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in temporal lobe epilepsy (TLE), executive dysfunction is also frequently documented (Dabbs *et al.*, 2009; Stretton and Thompson, 2012). Such findings challenge classical modular views of epilepsy-related cognition, in favour of conceptualizing these deficits in terms of 'networks' of neurocognitive substrates (Wilson and Baxendale, 2014). This concords with the new International League Against Epilepsy (ILAE) classification system characterizing focal epilepsy as a network disorder (Berg *et al.*, 2010; Kaaden *et al.*, 2011; Bernhardt *et al.*, 2015; Rayner and Tailby, 2017).

Focal epilepsy syndromes therefore represent ideal neuropathological models for investigating changes in cognition and associated unilateral network abnormalities. Language processing has received particular interest given its universality and well-established lateralization to the dominant hemisphere (Friederici, 2011). A wealth of research has demonstrated reorganization of language functions in TLE, including intra- and interhemispheric shifts in activation patterns associated with abstract word recognition (Pataraia *et al.*, 2004), verbal semantic decisions (Mbwana *et al.*, 2009; You *et al.*, 2011), covert verb generation (Liégeois *et al.*, 2004), and letter fluency (Brázdil *et al.*, 2005). These changes may be moderated by clinical factors, especially seizures with an earlier age of onset (Kwan and Brodie, 2001; Kaaden and Helmstaedter, 2009), higher frequency and severity (Hendriks *et al.*, 2004), and an associated greater resistance to anti-epileptic drugs (AEDs), often requiring polypharmacy (Kwan and Brodie, 2001; Ortinski and Meador, 2004; Hermann *et al.*, 2007).

Neuroplasticity of music cognition has been far less extensively investigated in epilepsy, despite proximal and partially overlapping fronto-temporal auditory brain networks with language (Brown *et al.*, 2006; Callan *et al.*, 2006; Besson *et al.*, 2007; Schön *et al.*, 2010; Wilson *et al.*, 2011; Merrill *et al.*, 2012). Given these parallels, evidence for epilepsy-induced language reorganization, and the effects of recurrent seizures on cognition more generally (Marques *et al.*, 2007; Kaaden and Helmstaedter, 2009; Tavakoli *et al.*, 2011), it may be reasonably argued that music functions are susceptible to similar neuroplastic mechanisms. This hypothesis, however, is challenged by the presumed greater bilaterality of music functions (Altenmüller, 2003; Wan and Schlaug, 2010; Wilson *et al.*, 2011; Merrett and Wilson, 2012). Although both music and language are bilaterally distributed, especially for early stages of auditory processing (Zatorre *et al.*, 2002; Hickok and Poeppel, 2004), music abilities appear less strongly lateralized for later stages of higher cognitive processing. Thus, tasks involving vocal or instrumental music perception and production primarily engage the fronto-temporal cortices, but also recruit widely distributed bilateral networks throughout the brain (Platel *et al.*, 2003; Brown *et al.*, 2004, 2006; Halpern *et al.*, 2004; Callan *et al.*, 2006; Stewart *et al.*, 2008; Wilson *et al.*, 2011). This raises the question of how recurrent unilateral seizures may affect a cognitive domain that is inherently bilaterally organized (Zatorre, 2005).

While the neuroplastic effects of epilepsy on music cognition remain unclear, a wealth of literature has documented training-induced reorganization of music functions in healthy individuals. Numerous structural and functional brain differences exist between musicians and non-musicians (Wan and Schlaug, 2010; Merrett and Wilson, 2012), including increases in regional cortical thickness and grey matter volumes (Gaser and Schlaug, 2003; Bermudez *et al.*, 2009) and enhanced white matter integrity (Steele *et al.*, 2013). These training-induced changes are hypothesized to confer benefits to non-music cognitive domains that demonstrate shared neural underpinnings, supporting the notion of 'near' and 'far' transfer in musicians for a range of cognitive skills (Wan and Schlaug, 2010; Moreno and Bidelman, 2014; Benz *et al.*, 2016), including general intelligence (Silvia *et al.*, 2016), verbal and working memory (Lee *et al.*, 2007; Cheung *et al.*, 2017), and executive functions (Degé *et al.*, 2011). Furthermore, in the neurorehabilitation literature musical elements (e.g. melody or rhythm) are incorporated to facilitate the engagement of damaged neural systems or homologous regions, such as those underpinning expressive language in stroke (Schlaug *et al.*, 2008; Norton *et al.*, 2009), or motor functions in Parkinson's disease (Benoit *et al.*, 2014; Dalla Bella *et al.*, 2015).

Evidence for cognitive and neural benefits in musicians raises the possibility of a neuroprotective effect of music training in the context of neurological disease. For instance, musicians with dementia have demonstrated preserved music performance abilities, memory for familiar musical material learned prior to disease onset, as well as memory for new material presented years after disease onset (Crystal *et al.*, 1989; Cowles *et al.*, 2003; Fornazzari *et al.*, 2006; Baird *et al.*, 2017). Musicians with herpes encephalitis have also illustrated remarkably preserved music skills despite severe verbal and visual amnesia (Cavaco *et al.*, 2012; Finke *et al.*, 2012). In the epilepsy domain, a professional singer with right TLE paradoxically showed improvement in singing pitch accuracy despite surgical resection of the right anterior temporal lobe, a crucial region for pitch discrimination, pitch-matching, and melodic memory (Wilson *et al.*, 2013). Similarly, Suarez *et al.* (2010) demonstrated preserved singing and humming abilities in a pianist with right TLE during direct electrocortical stimulation of right hemisphere regions that are critically involved in these abilities.

Other case studies have reported improved 'non-music' cognitive skills in musicians with epilepsy post-surgery. For example, following selective amygdalohippocampectomy, a musician with left mesial TLE displayed improved verbal and non-verbal memory (Trujillo-Pozo *et al.*, 2013), and a musician with right mesial TLE showed improved visual memory (Wieser and Walter, 1997). Collectively, investigations of musicians with neurological disorders support the idea that music functions may be resistant to the presence of neuropathology, possibly due to greater bilateral representation in the brain. However, despite a compelling account of training-related neuroprotection for both music and non-music abilities in some patients, few studies in epilepsy have compared music and non-music cognition in the same sample, combined with examining the influence of clinical epileptological variables and level of music expertise.

Thus, the aim of this study was to investigate the potential neuroprotective effects of music training by comprehensively profiling music versus non-music cognitive abilities in musicians and non-musicians with focal epilepsy, and control musicians and non-musicians. We predicted the highest performance across music and non-music tasks for control musicians, reflecting their neurologically healthy status in addition to potential cognitive transfer effects of their training (hypothesis 1). We predicted that musicians with epilepsy would perform the next best on music tasks given their training status, and comparably to control non-musicians for non-music cognition, reflecting the proposed benefits of music training in the context of neurological disease (hypothesis 2). Finally, we expected non-musicians with epilepsy to demonstrate the poorest performance for both music and non-music tasks, given their neurological status and the absence of significant music training (hypothesis 3).

In light of the well-documented influence of clinical epilepsy factors on cognition (particularly for language), we expected variables such as age of onset and epilepsy duration, seizure frequency and recency, and AEDs to be associated with non-music cognitive scores. Given the limited understanding of how these factors might relate to or influence music cognition, the present study aimed to explore these associations. In addition, given previous research demonstrating differential underlying patterns of neural dysfunction in left versus right focal epilepsy (Kemmotsu *et al.*, 2011; Besson *et al.*, 2014) and the well-established effects of seizure lateralization on verbal cognition, we accounted for this in our analysis of music and non-music cognition in musicians and non-musicians with epilepsy. Finally, given the interest in sensitive developmental periods in the literature, we explored whether the predicted cognitive transfer effects of music training were dependent on training age of onset, using a cut-off of $\leqslant 7$ years to distinguish 'early' and 'late' onset musicians (Penhune, 2011).

# Materials and methods

## Participants

Using G*Power, we calculated a required total sample of 50 participants to achieve 80% power in an analysis of covariance with $\alpha = 0.05$. We used the effect size provided in Henry and Crawford's (2004) meta-analysis of phonemic fluency (commonly assessed in TLE) in unilateral temporal lobe patients compared to healthy controls ($r = 0.44$, converted to effect size $f = 0.49$). This equated to a minimum of $n = 13$ each, for the groups of musicians and non-musicians with epilepsy, and control musicians and non-musicians. Given the paucity of available data comparing epilepsy patients and controls on music cognition, we increased the patient subgroups to a minimum of $n = 30$ to account for a potentially more conservative effect size. As described in the Results, we found no differences between non-musician and musician controls, thus these participants were combined into a single control group of $n = 33$.

The 74 patients with focal epilepsy included in the final sample comprised 35 musicians and 39 non-musicians (Table 1). They were recruited through the Comprehensive Epilepsy Program (Austin Health, Melbourne) while undergoing inpatient characterization of focal seizures, and from affiliated epilepsy outpatient clinics, between 2012 and 2015. Localization (temporal, frontal, parietal, or occipital lobe) and lateralization (left, right, or bilateral) of epileptogenic foci were achieved according to established methods from our group (Jackson *et al.*, 1990), including clinical history, ictal semiology, video-EEG monitoring, MRI, interictal $^{18}$F-fluorodeoxyglucose PET, ictal and interictal blood flow SPECT, and clinical neuropsychological evaluation. Exclusion criteria included: (i) IQ < 70; (ii) severe medical illness, other neurological conditions or previous neurosurgery; (iii) significant psychiatric history (not including mild depression or anxiety) or substance abuse; (iv) evidence suggesting amusia upon testing; and (v) being non-English speaking (see Fig. 1 for flow diagram of participant recruitment). The exclusion criterion of IQ < 70 reflects the ethics approvals granted to this study, in which individuals with an intellectual impairment were deemed unable to provide independent informed consent to participate in the research. Such individuals may also demonstrate difficulties comprehending the more complex cognitive tasks employed in this study, and warrant separate detailed investigation. No patient was diagnosed with musicogenic seizures. Participants who reported significant hearing difficulties underwent audiometric testing to ensure they demonstrated no more than mild (up to 40–45 dB) hearing loss in either ear. One patient had severe difficulties with the music tasks, likely indicative of amusia, with frustration and motivation issues resulting in early termination of testing.

Control participants were recruited during the same period as the patients and were sociodemographically-matched to the epilepsy group, comprising friends and family members of patients and associates of author L.J.B. Exclusion criteria were the same as for patients, with additionally no history of seizures. Of the initial sample of 35 assessed controls, two were excluded due to extremely poor performance on more than half of the music tests, likely indicative of amusia (Fig. 1). Thus, our final control sample comprised 33 individuals, including 13 musicians and 20 non-musicians (Table 1).

Participants were classified as musicians if they had more than 3 years of training or experience, in line with established criteria in the literature (Samson and Zatorre, 1988, 1991; Penhune *et al.*, 1999; Khalfa *et al.*, 2008; Wilson and Saling, 2008; Slater *et al.*, 2017). Supporting this, the total sample exhibited a median of 3 years of music training, indicating that non-musicians clustered around 0–3 years of training, while musicians spanned a range of 3–39 years. Musical

**Table 1 Demographic, clinical, and musical characteristics of the participants**

| | Non-musicians with epilepsy $n = 39$ | Musicians with epilepsy $n = 35$ | Control non-musicians $n = 20$ | Control musicians $n = 13$ |
|---|---|---|---|---|
| Age**, years, mean ± SD | 44.7 ± 14.5 | 35.7 ± 13.5 | 51.1 ± 14.5 | 40.2 ± 15.6 |
| Sex, $n$ (% female) | 19 (48.7) | 19 (54.3) | 15 (75.0) | 8 (61.5) |
| Education, years, mean ± SD | 13.4 ± 2.9 | 14.7 ± 3.2 | 14.7 ± 2.9 | 14.7 ± 2.6 |
| IQ*, mean ± SD | 103.0 ± 11.2 | 105.9 ± 9.8 | 110.3 ± 10.3 | 111.1 ± 10.3 |
| Handedness, % right: left: ambidextrous | 80: 10: 10 | 56: 12: 32 | 75: 10: 15 | 85: 8: 7 |
| Music experience, years, mean ± SD | 0.7 ± 1.2 | 9.7 ± 8.2 | 0.5 ± 0.8 | 9.3 ± 9.0 |
| Training onset, years, mean ± SD | 13.3 ± 7.3 | 9.7 ± 3.6 | 13.9 ± 8.2 | 9.2 ± 2.2 |
| Epilepsy factors | | | | |
| Onset, years, median (Q1, Q3) | 24.0 (12.8, 39.8) | 21.0 (15.2, 30.5) | – | – |
| Duration, years, median (Q1, Q3) | 12.0 (4.7, 27.8) | 8.0 (3.8, 16.0) | – | – |
| Months since last seizure, median (Q1, Q3) | 0.9 (0.1, 20.2) | 0.3 (0.1, 18.5) | – | – |
| Seizure frequency/month, median (Q1, Q3) | 1.0 (0.0, 4.0) | 2.5 (0.6, 6.0) | – | – |
| Seizure localization, % temporal focus[a] | 80 | 83 | – | – |
| Seizure lateralization, % left: right: bilateral: unknown | 49: 38: 8: 5 | 26: 49: 14: 11 | – | – |
| Pathology status, % MRI-positive | 33.3 | 54.3 | – | – |
| Anti-epileptic medications ($n$), median (Q1, Q3) | 1.0 (1.0, 2.0) | 2.0 (1.0, 3.0) | – | – |

*$P < 0.05$; **$P < 0.01$.
[a]Unknown seizure localization in $n = 1$ non-musician with epilepsy.

history was obtained via interview and the Survey of Musical Experience (Wilson *et al.*, 1999).

## Music cognitive tasks

### Montreal Battery of the Evaluation of Amusia

The Montreal Battery of the Evaluation of Amusia (MBEA, Peretz *et al.*, 2003) assesses melody discrimination using four subtests: (i) 'Scale', presence of an out-of-key note; (ii) 'Contour', pitch difference altering the original contour of the melody; (iii) 'Interval', pitch difference maintaining the original contour; and (iv) 'Rhythm', alteration of rhythmic contour. The MBEA also assesses identification of musical beat ('Metre'), and incidental recognition memory ('Recognition') (see Supplementary Table 1 for a summary of music tasks).

### Pitch discrimination and memory

We administered a computerized just noticeable difference (JND) task of fine-grained pitch discrimination with frequency (Hz) manipulations of 1%, 2.5%, 5%, 10%, and 20% higher or lower than the original pitch. Zatorre and Samson's (1991) pitch working memory task assessed pitch discrimination ability with auditory interference.

The musical paired associate learning (MPAL) task (Wilson and Saling, 2008) assessed semantic and arbitrary relational learning of short paired melodic motifs across three trials, and recognition memory after each trial in a three-alternative forced-choice paradigm. Two versions of this task have been developed: (i) a familiar/unfamiliar MPAL task, where the paired motifs to be remembered are taken from either familiar tonal melodies (e.g. Wagner's *Wedding March* from Lohengrin) or novel tonal melodies matched to the style of the familiar stimuli; and (ii) a tonal/atonal MPAL task, where all motifs are novel but half conform to a Western tonal framework and half are atonal.

## Non-music cognitive tasks

A comprehensive battery of well-validated neuropsychological tests routinely used in people with epilepsy comprised the non-music cognitive assessment (Supplementary Table 2). This included tests of general intellect, attention and speed of processing, executive functioning, language, memory, and visuospatial processing.

### Procedure

The study was approved by the Human Research Ethics Committees of Austin Health (Melbourne) and The University of Melbourne. All participants gave written informed consent in accordance with the Declaration of Helsinki.

Epilepsy inpatients ($n = 30$) were tested at their bedside during video-EEG monitoring. All efforts were made to reduce noise and distractions. Outpatients ($n = 44$) and controls ($n = 33$) were tested in a quiet room, seated at a desk. Music stimuli were played to participants through over-the-ear headphones from a laptop computer, and responses either written down or verbally given to the examiner (L.J.B.). The examiner listened through an additional pair of headphones during all tasks to ensure understanding of and compliance with instructions. Non-music tasks were administered according to standardized instructions. Following completion of the demographic and music questionnaires, participants were introduced to the tasks in an alternating fashion to avoid overloading them with the musical stimuli. Breaks were provided as necessary, and some participants completed the testing across multiple sessions. Average testing time was 4 h.

## Statistical analysis

Statistical analyses were performed with SPSS Version 24, using an alpha level of $P < 0.05$ to determine significance.

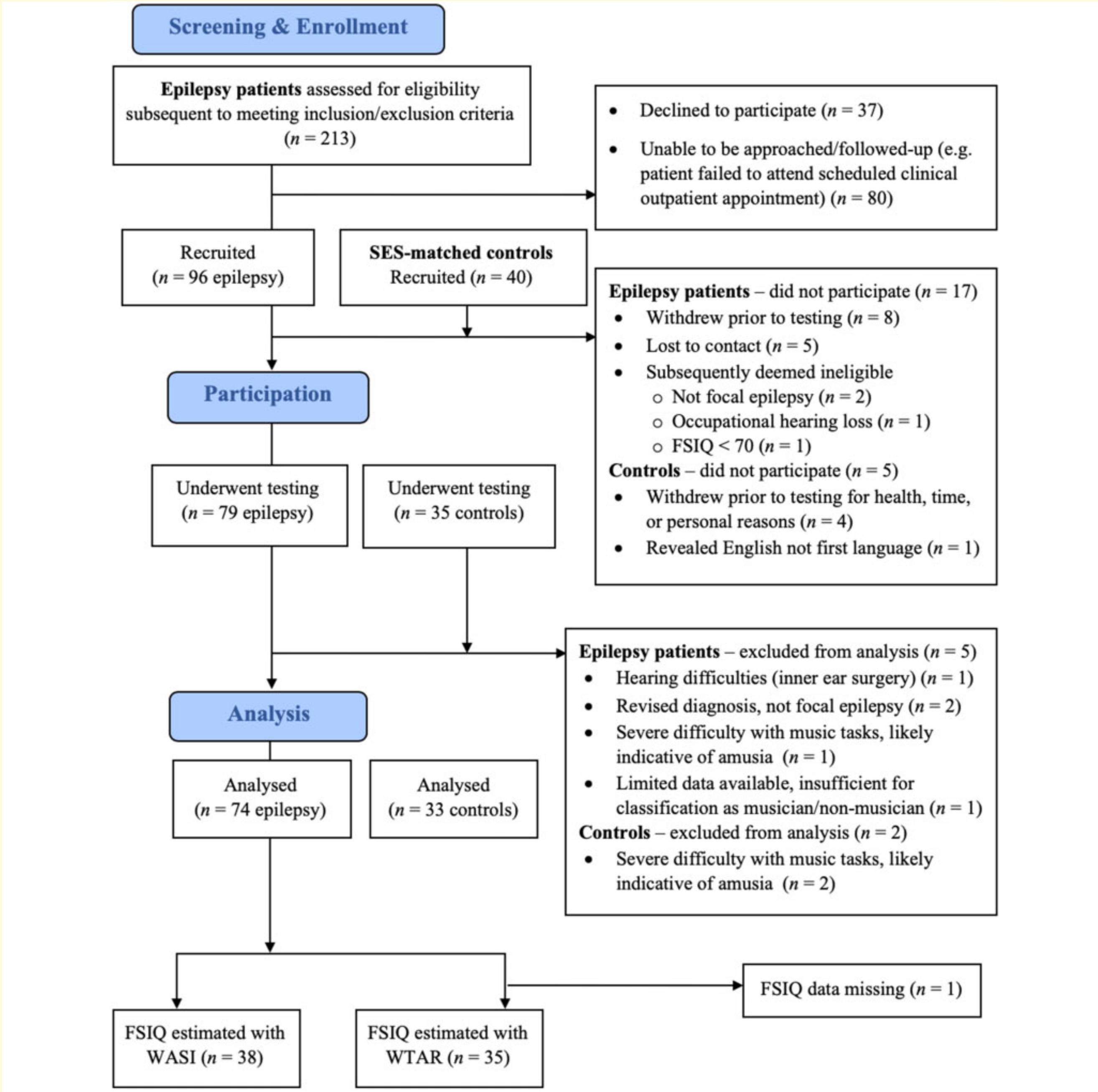


**Figure 1 Flow diagram of participant recruitment.** Flow diagram summarizing the processes of screening, recruitment, and analysis of participants in the study, including reasons for participant exclusions at each study phase. Diagram based on the 2010 CONSORT (Consolidated Standards of Reporting Trials) template (Moher *et al.*, 2001).

Raw scores for music and non-music tasks were converted to age-, gender-, and (where available) education-adjusted *z*-scores. Non-music normative data were predominantly sourced from Strauss *et al.* (2006). No normative data were available for delayed free recall of the Verbal Paired Associate Learning (VPAL) task. Since large, published normative datasets have not been established for most of the music tasks, unpublished data obtained via the test authors were used where available. Standardized sensitivity values ($d'$) were calculated for the JND using Corwin's (1994) formula.

Overall, there were 16 music test scores and 17 non-music test scores for each participant. Across 14 control participants, 4.5% of all individual test scores fell $>2$ standard deviations below the mean and thus were winsorized to 2 standard deviations rather than excluded, to minimize any bias on the mean and to retain as large a control sample as possible (Tabachnick and Fidell, 2013). Similarly, all missing data were excluded pairwise rather than listwise. To minimize the risk of type I error, the individual test scores were combined to create composite scores measuring core cognitive domains, consistent with the guidelines of Wilson *et al.* (2015). The non-music composite scores comprised verbal cognition, non-verbal cognition, executive function, verbal learning and memory, and non-verbal learning and memory (Supplementary Table 5). Four of the non-music tests [Matrix Reasoning, Vocabulary, and Block Design subtests of the Wechsler Adult Intelligence Scale/Wechsler Abbreviated Scale of Intelligence (WAIS/WASI), and delayed free recall of the VPAL task] were analysed separately as they had a higher rate of missing data, and Full Scale IQ was included as a covariate as described below. The music composite scores comprised 'global' music ability (averaged across all music scores), frequency discrimination, melodic processing, rhythmic processing, pitch working memory, and melodic learning and memory. All composite scores demonstrating significant skewness or kurtosis ($|z| > 1.96$) were submitted to a Box-Cox transformation (Osborne, 2010) to meet assumptions for parametric statistical testing.

One-way ANOVAs with Tukey's HSD *post hoc* comparisons, and chi-square tests were performed to assess demographic differences between groups (Table 1). Musicians with epilepsy were the youngest group [$F(2,104) = 5.68$, $P = 0.005$] compared to non-musicians with epilepsy ($P = 0.025$) and controls ($P = 0.006$). There was a significant main effect of IQ [$F(2,100) = 4.43$, $P = 0.014$] and although subgroup comparisons were not significant, subsequent analyses included IQ as a covariate. There were no group differences in sex or handedness, nor did musicians and non-musicians with epilepsy differ for left- versus right-hemisphere seizure lateralization. However, given the lower percentage of musicians with left-hemisphere epilepsy (Table 1), we conservatively included a dummy-coded variable for left-hemisphere seizure lateralization as a covariate in the analyses.

To test hypotheses 1–3, we ran a series of one-way ANCOVAs comparing the groups on the five non-music and six music composite scores. To investigate group differences, *post hoc* pairwise comparisons of estimated marginal means were conducted with Sidak corrections for multiple comparisons, which are more conservative than Tukey's LSD (Field, 2009). As all clinical epileptological variables were non-normally distributed, associations between these factors and the music and non-music cognitive composite scores were examined using Kendall's tau-b ($\tau_b$) bivariate correlations. Only correlations $\geqslant |0.20|$ were considered to represent meaningful effect sizes with practical interpretability (Ferguson, 2009) and thus, correlations below this recommended value are not reported in the 'Results' section. To explore the effects of music training onset, we ran a series of ANCOVAs between 'early' and 'late' musicians, compared to non-musicians. For this latter set of analyses, patient and control groups were collapsed as we were primarily interested in the effects of training onset. These three groups did not differ in IQ, and the 'early' and 'late' musicians shared similar total years of music experience.

# Data availability

Anonymized data will be made available to qualified researchers upon reasonable request.

# Results

## Primary analyses

### Profiling non-music and music cognition in non-musicians and musicians with epilepsy

Standardized performance profiles for the non-music and music composite scores as well as the individual test scores are shown in Figs 2 and 3. The overall patterns displayed by these profiles generally conformed with the study predictions. Healthy controls mostly displayed the highest performance. Next were musicians with epilepsy, while non-musicians with epilepsy demonstrated the largest deficits relative to the other two groups.

Parametric analyses showed significant group differences for the composite scores of verbal cognition [$F(2,98) = 3.66$, $P = 0.029$, $\eta^2_{\text{partial}} = 0.07$], non-verbal cognition [$F(2,97) = 2.11$, $P = 0.036$, $\eta^2_{\text{partial}} = 0.07$], and executive function [$F(2,97) = 6.95$, $P = 0.002$, $\eta^2_{\text{partial}} = 0.12$]. Pairwise comparisons of estimated marginal means revealed a specific verbal cognitive impairment in non-musicians with epilepsy compared to controls ($P = 0.026$). For non-verbal cognition, subgroup comparisons approached significance for non-musicians with epilepsy compared to controls ($P = 0.065$) and musicians with epilepsy compared to controls ($P = 0.059$). For executive function, both non-musicians ($P = 0.001$) and musicians ($P = 0.042$) with epilepsy performed significantly below controls (Fig. 4). No significant group differences were found for the music composite scores, or for the four non-music variables with higher rates of missing data that were analysed separately.

## Secondary analyses

### Associations between clinical epilepsy variables and cognition

As illustrated schematically in Fig. 5, poorer performance on the composite score of executive function was associated with greater anti-epileptic polypharmacy ($\tau_b = -0.22$, $P = 0.015$). As age of onset was strongly associated with disease duration ($\tau_b = -038$, $P < 0.001$), a frequent confounding parameter, Pearson partial correlation analyses were performed controlling for epilepsy duration. This showed that younger age of onset was associated with poorer performance on the composite score of non-verbal cognition ($r = 0.28$, $P = 0.02$), but higher performance for melodic learning and memory ($r = -0.25$, $P = 0.036$). Longer disease duration was associated with poorer pitch working memory, controlling for age of onset ($r = -0.25$, $P = 0.039$).

### Influence of onset of music training on cognition

Figure 6A shows standardized performance profiles for the early- and late-onset musicians, and non-musicians, across

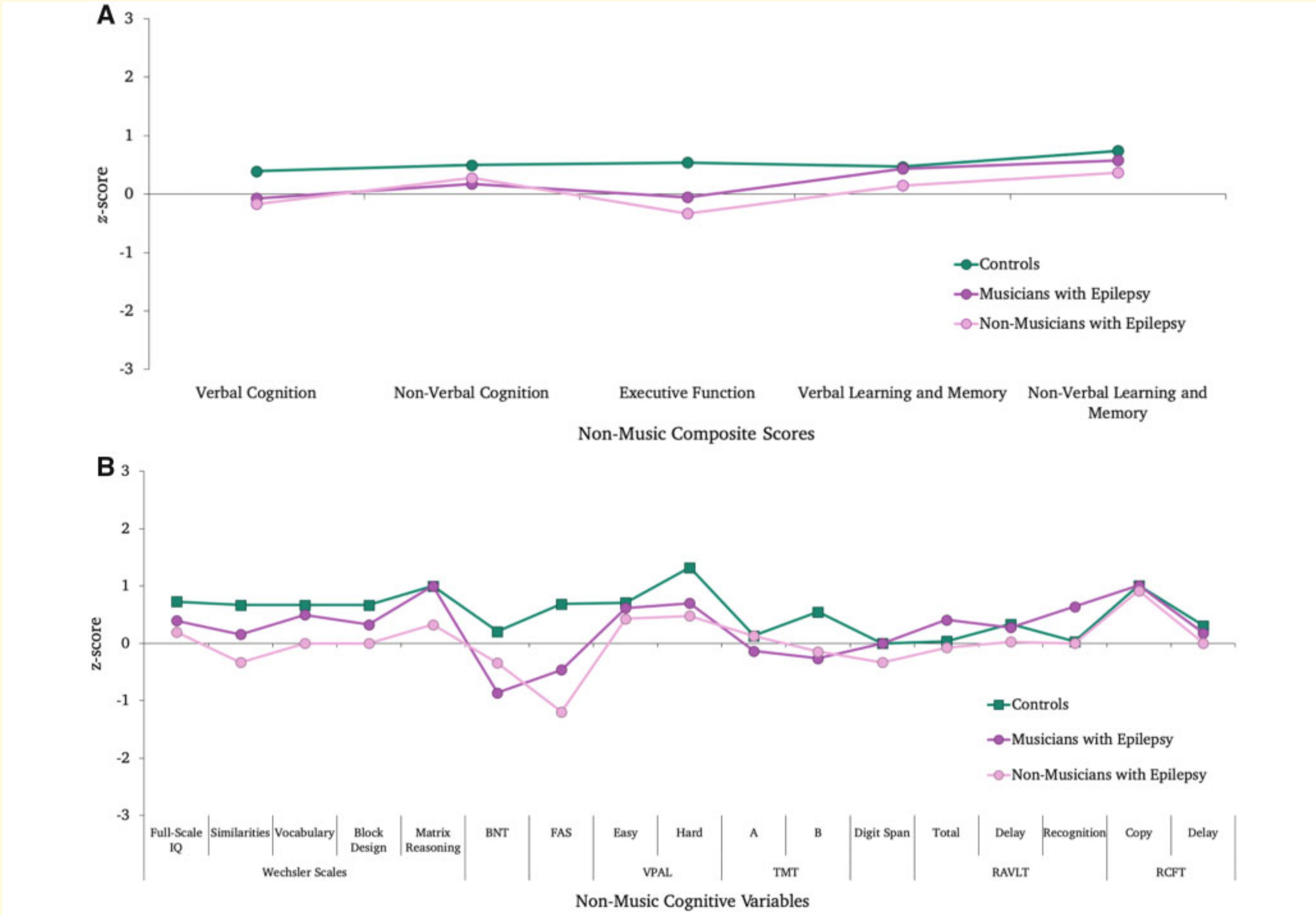


**Figure 2 Standardized performance profiles for non-music composite scores and all non-music cognitive variables across groups.** Profile plots of median z-scores (untransformed) for each non-music composite score (**A**) and individual non-music cognitive variables (**B**), across the groups. Overall, the two patient groups mostly displayed lower non-music performance profiles relative to the combined control group. A clearer separation between musicians and non-musicians with epilepsy was observed across the individual non-music variables. Notably, IQ was in the normal range for all groups (**B**). BNT = Boston Naming Test; FAS = letter fluency for F, A, S; RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test; TMT = Trail Making Test; VPAL = Verbal Paired Associate Learning.

the non-music and music composite scores. Overall, the pattern of effects supported better performance of the early-onset musicians, compared to both late-onset musicians and non-musicians. This was predominantly evident for the music composite scores, reaching significance for melodic learning and memory [$F(2,103) = 3.41$, $P = 0.037$, $\eta^2_{partial} = 0.06$], and carried by better performance of the early-onset musicians compared to non-musicians ($P = 0.04$; Fig. 6B). As illustrated by Fig. 6A, the early-onset musicians also appeared to perform better than late-onset musicians and non-musicians on the verbal cognition composite score; however, this difference did not reach significance. We note that these analyses were limited by the small and unequal subgroup sizes ($n = 15$ early-onset musicians, $n = 33$ late-onset musicians, and $n = 59$ non-musicians), warranting caution in interpreting these differences.

# Discussion

This study aimed to comprehensively profile music and non-music cognition in patients with focal epilepsy compared to healthy controls, and to investigate the extent to which music training is neuroprotective. Regarding our first hypothesis, although control musicians tended to display the highest scores across tasks, their performance did not significantly differ from control non-musicians. Our second hypothesis was supported; musicians with epilepsy were comparable to combined controls on composite scores of verbal and non-verbal cognition, and verbal and non-verbal learning and memory, but impaired on executive function. Supporting hypothesis 3, non-musicians with epilepsy were the poorest performing group, with significant deficits in verbal cognition and executive function relative to controls. Clinical epilepsy variables reflective of the severity of illness

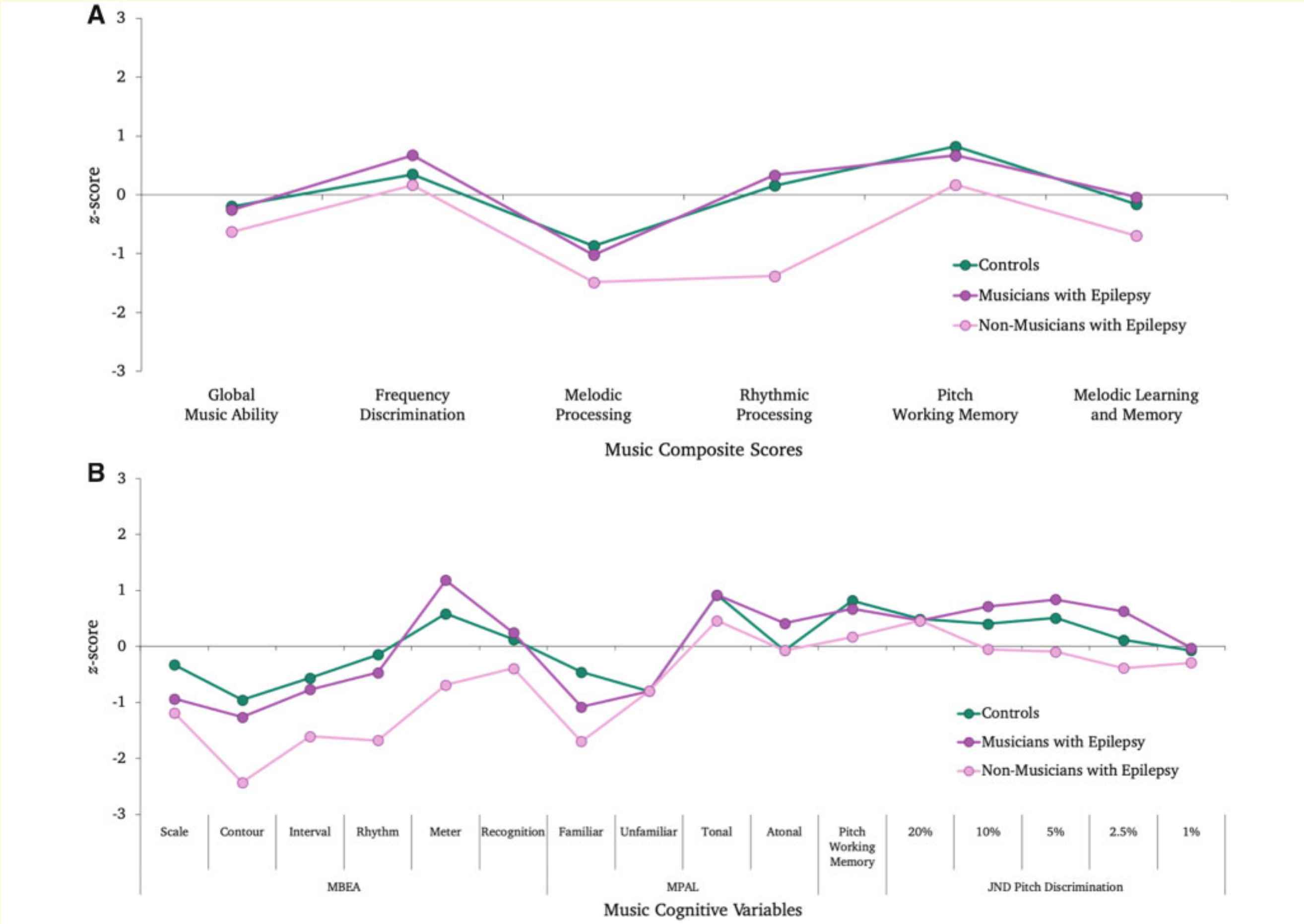


**Figure 3 Standardized performance profiles for music composite scores and cognitive variables across groups.** Profile plots of median z-scores (untransformed) for each music composite score (**A**) and individual music cognitive variables (**B**), across the groups. Overall, non-musicians with epilepsy performed the poorest across both composite scores and individual variables, while musicians with epilepsy performed more similarly to the combined control group. JND = just noticeable difference; MBEA = Montreal Battery of Evaluation of Amusia; MPAL = Musical Paired Associate Learning.

(duration of epilepsy, polypharmacy) were correlated with poorer music (pitch working memory) and non-music executive function scores, but demonstrated variable findings for age of epilepsy onset. In addition, musicians who began training earlier in life tended to show greater benefits for melodic learning and memory, with a trend suggestive of relatively enhanced verbal cognitive skills.

These findings suggest a neuroprotective effect of music training against the cognitive sequelae of focal epilepsy; specifically, a selective preservation of verbal cognition. We propose a model of factors interacting along three key dimensions (Fig. 7), with specific cognitive outcomes resulting from the interaction between two or more dimensions: disease status (epilepsy versus control), music expertise (musician versus non-musician), and cognitive domain (music versus non-music). For example, under disease status we observed overall greater cognitive impairment in epilepsy patients versus controls, and under music expertise we observed general cognitive benefits in musicians. The junction between these two dimensions reflects our specific finding of cognitive impairments in non-musicians with epilepsy. We discuss the key findings below with these interactions in mind.

## Music training appears neuroprotective for verbal cognition

Our finding of impaired verbal cognition in non-musicians with epilepsy reflects the ultimate interaction between disease status, music expertise, and cognitive domain (Fig. 7, middle). This implicates the possible neuroprotective effects of training-induced neuroplasticity, against the detrimental impact of epileptogenic neuropathology and/or recurrent seizure activity. It concords with studies demonstrating preservation of verbal cognition in musicians with epilepsy (Suarez *et al.*, 2010; Hegde *et al.*, 2016), cerebral infarction (Wilson, 1996; Terao *et al.*, 2006), dementia (Baird *et al.*, 2017), and herpes encephalitis (Cappelletti *et al.*, 2000).

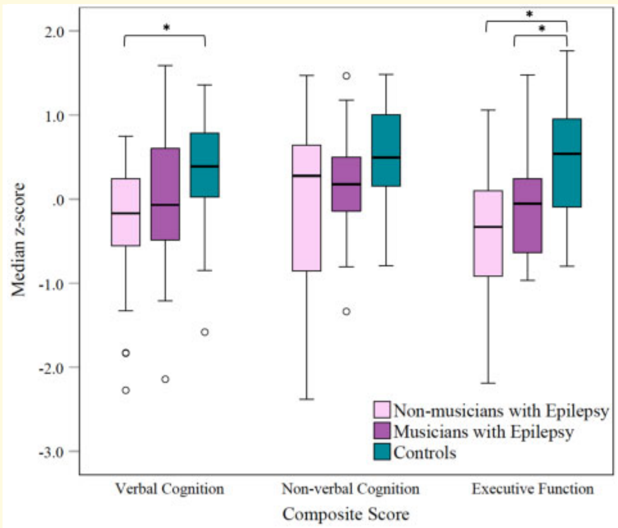


**Figure 4 Specific verbal cognitive deficits in non-musicians with epilepsy in the context of broader executive dysfunction.** Non-musicians with epilepsy performed significantly poorer than the combined control group on the verbal cognition composite score. Parametric analyses also revealed a significant group effect for non-verbal cognition; however, subgroup comparisons did not reach significance. Both non-musicians and musicians with epilepsy performed poorer than controls on the composite score of executive function, however, we observed a similar trend of the lowest scores in non-musicians with epilepsy, and relatively higher performance in musicians with epilepsy. The groups did not significantly differ in their music composite scores. Asterisks denote significant group comparisons.

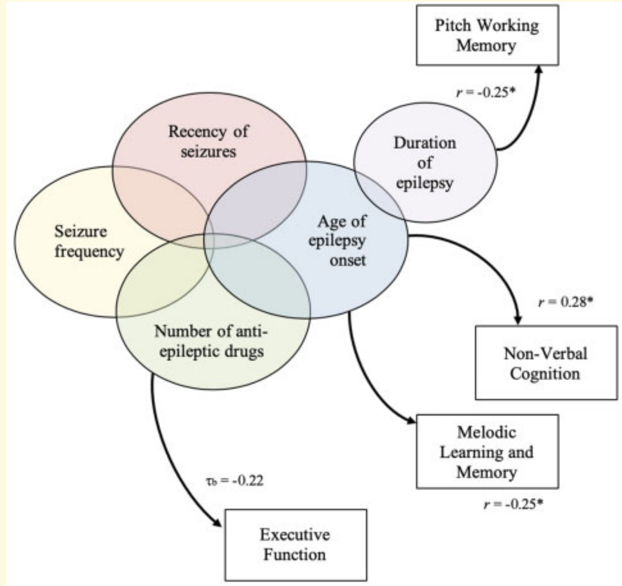


**Figure 5 Significant correlations between epilepsy variables and music and non-music composite scores.** Schematic illustration of significant correlations ⩾|0.20| between clinical epilepsy variables and music and non-music composite scores. The overlapping ellipses represent significant correlations among the clinical epilepsy variables. In general, variables reflecting the severity of illness (e.g. duration of epilepsy and number of AEDs) were associated with poorer cognitive performance. Kendall's tau-b correlation coefficient is noted for the association between AEDs and Executive Function, and Pearson *r* is noted (asterisk) for the partial correlations controlling for epilepsy duration or age of onset.

These verbal cognition benefits might be explained by mechanisms of 'near' transfer. That is, music training-induced enhancement of domain-general neural resources supporting auditory cognitive processes required for both music and verbal tasks (Li *et al.*, 2008; Patel, 2012; Peretz *et al.*, 2015).

In particular, our finding of preserved verbal cognition (including elements of executive function) but not executive function *per se* in musicians with epilepsy suggests a potential temporal lobe specificity of music training-induced neuroplasticity, which may facilitate near transfer effects for non-music skills. For instance, music expertise is associated with superior discrimination of frequency and pitch, temporal duration and rhythm, melody, and harmony (for a review see Besson *et al.*, 2011). Musicians have also demonstrated enhanced detection of, and electrocortical responses to, subtle spectral and temporal manipulations in speech (Besson *et al.*, 2011). These behavioural and electrophysiological findings may reflect neuroanatomical differences in the auditory cortices of musicians and non-musicians, such as increased cortical thickness in regions along the superior temporal plane and higher grey matter concentration in Heschl's gyrus, particularly on the right side (Bermudez *et al.*, 2009).

Music expertise has also been associated with macro- and microstructural white matter changes. Larger tract volume and stronger directionality of water diffusion along axons (typically reflecting greater tract integrity) have been identified in the arcuate fasciculus—a major fronto-temporal pathway—in singers and instrumental musicians compared to non-musicians (Halwani *et al.*, 2011). Consistent with this potential strengthening of fronto-temporal white matter tracts, musicians have demonstrated increased cortical thickness in middle and ventrolateral frontal regions bilaterally, in addition to more extensive thickness increases in the right pars triangularis and middle frontal pole (Bermudez *et al.*, 2009). The arcuate fasciculus has been associated with greater sensitivity to, and control of, musical pitch (Loui *et al.*, 2009) in addition to supporting language production (Bonilha and Fridriksson, 2009; Marchina *et al.*, 2011) and word learning (López-Barroso *et al.*, 2013). Research has also shown that the integrity of the arcuate fasciculus is affected in patients with TLE (Burzynska *et al.*, 2011; Pustina *et al.*, 2015). Thus, it is plausible to hypothesize that music training-related enhancements in the structural integrity and functional efficiency of the temporal lobes and their major connections may assist in counteracting the adverse effects that TLE has on these same neural networks. With shared reliance of music and verbal cognitive skills on these auditory networks, a musician advantage would likely benefit functions

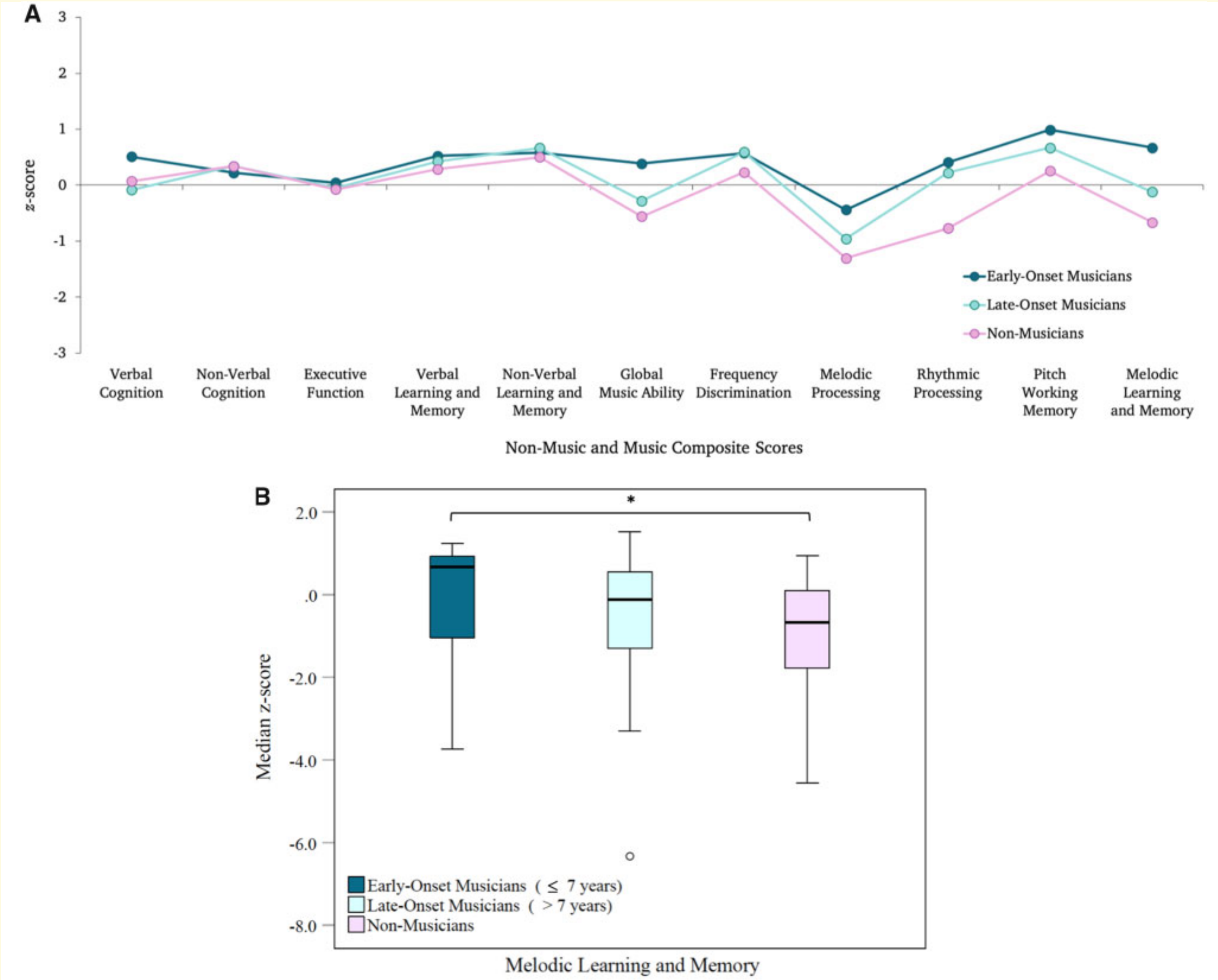


**Figure 6 Standardized performance profiles for non-music and music composite scores across early-onset and late-onset musicians, and non-musicians and training onset effects for melodic learning and memory composite score.** Profile plots of Median z-scores (untransformed) for non-music composite scores (**A**) demonstrate relatively higher performance in early-onset musicians, for most music variables in addition to verbal cognition. This difference only reached significance for the composite of melodic learning and memory (**B**), specifically for the comparison of early-onset musicians versus non-musicians. (**B**) Box plots with the median are represented by the thick black lines, and whiskers represent first and third quartiles. Asterisk denotes significant group comparison.

in both domains, providing a possible explanation for the preserved verbal cognition observed in our musicians with epilepsy.

The idea that music training also enhances basic auditory attention and memory processes is supported by our finding of an early training onset advantage for melodic learning and memory. Although there were no significant effects of training onset on non-music cognitive abilities, this finding, in addition to the numerically higher scores on the verbal cognition composite in early-onset musicians, is broadly consistent with previous work investigating the cognitive benefits of skill enrichment during sensitive neurodevelopmental periods (Penhune, 2011; Skoe and Kraus, 2013; Steele *et al.*, 2013). Notably, this early neuroplastic period also increases the brain's vulnerability to network disruption, illustrated by the association between younger age of seizure onset and reduced white matter connectivity in TLE (Kemmotsu *et al.*, 2011). Although speculative, music training during sensitive developmental windows may therefore be more effective in preventing or attenuating concomitant seizure-related dysfunction. A limitation of our early- versus late-musician comparison, however, was the unequal sample size and small number of epilepsy patients in the early-onset musician group ($n = 11$), precluding robust examination of this issue in the present study. Nonetheless, since the early- and late-musicians with epilepsy did not differ in training duration, we believe that in a larger sample, these training-onset advantages for

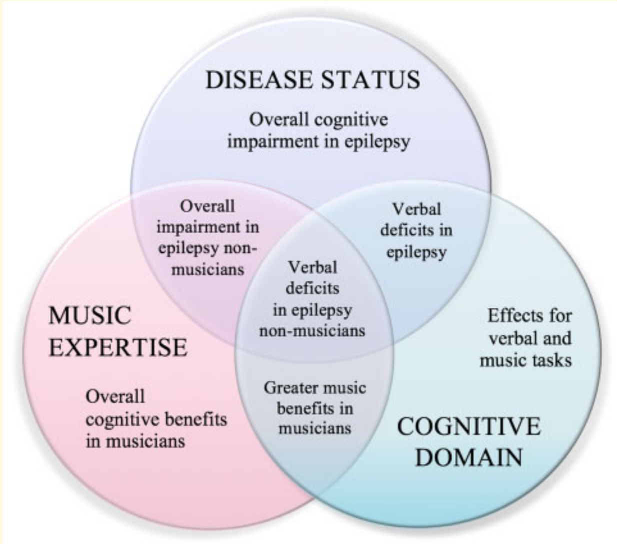


**Figure 7 Interactions between the effects of disease status, music expertise, and cognitive domain.** Schematic representation of the independent effects of disease status (patient versus control), cognitive domain (music versus non-music), and music expertise (musician versus non-musician), and their combined and interactive effects.

working memory and verbal cognition may be more pronounced.

The musicians with epilepsy began training, on average, 13.5 years prior to seizure onset, implying that potential underlying neuroplastic changes supporting transfer effects may have already taken place. This finding should motivate future work to investigate the effectiveness of training-induced neuroplasticity in the context of pre-existing dysfunction, as has been extensively investigated in the cerebrovascular literature via melodic intonation therapy for language rehabilitation following stroke (Norton *et al.*, 2009; Merrett *et al.*, 2014). There is a further need to qualify and quantify the longevity or stability of training-induced neuroplasticity (Skoe and Kraus, 2012), considering only 65% of our patient musicians and 77% of control musicians were currently musically active. We also acknowledge that socioeconomic status was not explicitly assessed, even though the control group was sociodemographically-matched through recruiting family members and friends of the epilepsy patients. Recent research has demonstrated associations between predisposing factors (e.g. personality and socioeconomic variables) and cognition in children who enrol in music training (Corrigall *et al.*, 2013; Corrigall and Schellenberg, 2015). Thus, we cannot completely rule out the possibility that socioeconomic status may have exerted an effect on our findings. While the purpose of the current study was to provide to an initial characterization of music and non-music cognitive profiles in people with epilepsy, future research should investigate the possible impact of additional variables such as socioeconomic status and personality factors.

Structural and functional neuroimaging evidence is also essential for validating potential neuroplastic changes in musicians and the corresponding relationship with cognitive performance. This is a critical next step for research investigating epilepsy musicians, to disentangle the possible neuroplastic effects of music training from epileptogenic processes, such as seizure-induced intra- or interhemispheric functional reorganization as described in the language domain. An extension of our cognitive findings may inform epilepsy surgery practice, particularly regarding the risks of post-surgical cognitive dysfunction in musicians versus non-musicians with epilepsy.

## Greater resistance to neurological disruption for music compared to language

Our results illustrated greater resistance of music functions to the effects of neurological abnormality compared to non-music abilities (overlap of disease status and cognitive domain in Fig. 7). While non-musicians with epilepsy generally displayed the poorest performance across both non-music and music cognitive domains (overlap of disease status and music expertise), these effects were only significant for non-music composite scores assessing verbal cognitive abilities and executive function. This builds upon evidence for greater bilateral representation of music functions in the brain (Altenmüller, 2003; Zatorre, 2005; Wan and Schlaug, 2010; Merrett and Wilson, 2012), contrasting with the more vulnerable left-lateralized language network (Friederici, 2011). Importantly, the greater relative deficits in verbal cognition in non-musicians with epilepsy did not appear to be driven by greater left-hemisphere seizure lateralization in this group compared to the musicians with epilepsy, as left-hemisphere lateralization was controlled across analyses. It will be important to replicate these findings in larger samples to validate and further refine the differential cognitive profiles of musicians and non-musicians with left- and right-sided seizure foci.

Our correlational results were consistent with previous findings indicating that poorer cognitive outcomes are associated with greater disease severity, as reflected by longer epilepsy duration, and treatment with polypharmacy for seizure control (Kwan and Brodie, 2001; Ortinski and Meador, 2004; Hermann *et al.*, 2007). Although studies have also reported adverse effects of a younger age of seizure onset (Kwan and Brodie, 2001; Kaaden and Helmstaedter, 2009), we only observed this effect for non-verbal cognitive scores, while the reverse association emerged for the composite score of melodic learning and memory. We cautiously suggest that music training onset may confound this relationship given the significant difference between early-onset musicians and non-musicians on their composite scores of melodic learning and memory. Indeed, when age of music training onset was taken into account, the association with seizure onset was no longer evident.

## Limitations and directions for future research

The overall proportion of left- versus right-sided seizure foci in our sample did not differ, and we controlled for left-hemisphere seizure lateralization across analyses, making it unlikely that our results are due to a broader lateralization bias. However, the epilepsy group predominantly comprised patients with temporal lobe seizure foci, limiting the power of our study to determine the extent of cognitive impairment associated with seizures arising outside of the temporal lobe. Future studies should aim to recruit more patients with non-temporal lobe seizures, particularly those with frontal lobe foci given the conceptualization of focal epilepsy as a disorder of extensive, fronto-temporal networks (Dabbs *et al.*, 2009; Rayner and Tailby, 2017).

A further limitation of our study is the exclusion of epilepsy patients with intellectual impairment, who represent an important subgroup requiring specific characterization of their music versus non-music cognitive profiles. Future detailed investigation of this subgroup will ensure the generalisability of cognitive findings across the broader epilepsy population. The study design was also limited by the fact that some epilepsy patients had already undergone recent clinical neuropsychological assessment, including estimation of IQ by the Wechsler Test of Adult Reading (WTAR; The Psychological Corporation, 2001) rather than the WASI (Wechsler, 1999). Although these participants did not differ significantly in their estimated IQ, ideally, variability in tests within a patient cohort should be minimized to reduce potential confounds. Furthermore, we note that patients may have had their medication doses varied contemporaneous with their participation in the study, particularly those undergoing inpatient monitoring for seizure characterization.

Finally, while our study was not powered to compare lesion-negative versus lesion-positive subgroups of left- and right-sided epilepsy patients, this would be a valuable comparison in a larger sample, to further examine whether differing patterns of network disruption (Vaughan *et al.*, 2016) are associated with distinct cognitive profiles within an otherwise relatively homogenous neurological population.

# Conclusions

This study provides evidence for a possible neuroprotective effect of music training against the cognitive sequelae of focal epilepsy, particularly the effects of seizures on verbal cognition. Musicians with epilepsy possessed an average of just under 10 years of music experience, with a range of 3.5 to 39 years, inciting future research to validate the level of musical expertise that may be sufficient for advantageous skill transfer and associated neuroplastic changes. Furthermore, our results suggest that training-related neuroprotection may not be completely contingent on current musical engagement, and that lifetime involvement in performing music might provide neurocognitive benefits. We contribute to the evidence that music training commencing earlier in life may result in greater cognitive advantages. The implications are clear from a pedagogical perspective, highlighting the need for ongoing efforts around increasing access to, and engagement with, musical training in children (Lamont *et al.*, 2003; Wright, 2008; McPherson *et al.*, 2015). Extending this to clinical practice, music training may prove a useful adjunct treatment for individuals diagnosed with epilepsy, potentially offsetting its adverse cognitive effects, particularly for those at a higher risk of epileptogenesis, such as children with a family history of epilepsy (Berkovic *et al.*, 1998; Abou-Khalil *et al.*, 2007; Weckhuysen *et al.*, 2016). Finally, we demonstrated that focal epilepsy syndromes were less detrimental to music perception abilities than non-music cognition, highlighting the potential benefits of bilateral cerebral representation of music functions. Conversely, the overall pattern of music and non-music cognitive difficulties in our non-musicians with epilepsy corroborates modern notions of broader network-based disease in epilepsy (Berg *et al.*, 2010; Bernhardt *et al.*, 2015; Rayner and Tailby, 2017).

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# Competing interests

The authors report no competing interests.

# Supplementary material

Supplementary material is available at *Brain* online.

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