Neuroplastic effects of music lessons on hippocampal volume in children with congenital hypothyroidism

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Children with congenital hypothyroidism (CH) who experience a neonatal thyroid hormone deficiency have reduced hippocampal volumes compared with healthy controls. Interestingly, evidence suggests that musical training can contribute to structural plasticity in a number of brain areas, including the hippocampus. Therefore, we investigated whether taking music lessons could ameliorate the volumetric reductions of the hippocampus in children with CH. Left and right hippocampal volumes were measured in four groups of children: children with CH with and without music lessons, and healthy controls with and without music lessons. We found that the volume of the right hippocampus was comparable between children with CH who had taken music lessons and the healthy controls. Children with CH who had not taken music lessons had reduced hippocampal volumes compared with the other three groups. These results suggest that music lessons may induce structural neuroplasticity in children with atypical hippocampal development because of early thyroid hormone deficiencies. *NeuroReport* **00:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The hippocampus is a medial temporal structure that is critical for memory, spatial learning, and novelty detection [1–3]. Extensive research on animals has shown that the hippocampal structure and function are particularly vulnerable to early thyroid hormone (TH) deficiency [3–6]. Specifically, a deficiency of TH during gestation and early infancy is known to impair neurogenesis, synaptic function, and dendritic growth within the hippocampus, leading to deficits in spatial learning and memory [3–7]. A recent study has shown that children with congenital hypothyroidism (CH), who experience TH deficiency during late gestation and early postnatal life, have reduced hippocampal volumes relative to typically developing controls [8]. In addition, these children show relative weaknesses in learning and memory, as well as abnormal hippocampal activation during fMRI tasks that are critically dependent on the hippocampus [9,10]. Thus, TH appears to be essential for normal hippocampal development in humans.

It is well known that the hippocampus is also highly susceptible to experience-dependent neuroplasticity. In animals, prenatal exposure to music can enhance neurogenesis in the hippocampus and improve spatial memory [11]. In humans, musical training is associated with higher gray matter density within the hippocampus, in addition to structural enhancements in other brain regions including the precentral and superior temporal gyri [12,13]. Moreover, functional activations within the hippocampus during both memory retrieval and temporal novelty tasks are larger in musicians relative to nonmusicians [13,14]. Consistent with these findings, it has been shown that musicians have enhanced working memory [15,16] and long-term memory [17] compared with nonmusicians.

Given that hippocampal volume is reduced in children with CH and enhanced in musicians, we investigated the possibility that music lessons could induce structural neural plasticity in an abnormally developing hippocampus. Specifically, we measured the influence of music lessons on hippocampal volumes in children with CH relative to controls. It is likely that some of the structural abnormalities in the hippocampus of children with CH will be ameliorated in children with CH who have taken music lessons.

Materials and methods

Participants

Participant demographics are presented in Table 1. All participants were originally part of other studies on memory and the hippocampus [8,9]. The CH participants were initially recruited from either: (a) a longitudinal cohort identified at birth through the Ontario newborn thyroid-stimulating hormone screening program and followed at the Hospital for Sick Children (Sickkids), or (b) the Endocrine Clinic at Sickkids. All CH participants had elevated thyroid-stimulating hormone levels at birth, indicating a period of TH insufficiency during late gestation and early life until treatment was provided. Controls were recruited from our participant

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database and the majority were also part of the same longitudinal cohort as the children with CH. Exclusion criteria for all participants were as follows: head injury, chronic medical condition, neuroradiological abnormality, or an IQ score below 80. Additional exclusionary criteria for controls were as follows: an identified learning disability or a diagnosis of attention deficit hyperactivity disorder.

Study design

All parents provided written consent and all participants provided oral consent for their participation in the larger cohort study. Demographic data [age, sex, socioeconomic status (SES)], IQ scores (WASI), and information from a musical training questionnaire were obtained from data collected during the larger cohort studies. Participants were then divided into four groups: (a) CH without music lessons (CH-NoMus), (b) CH with music lessons (CH-Mus), (c) controls without music lessons (Con-NoMus), and (d) controls with music lessons (Con-Mus) (Table 1). All participants in the musical training groups had at least 1 year of music lessons. All procedures were approved by the Research Ethics Board of Sickkids and the Office of Research Ethics at the University of Toronto.

Scanning

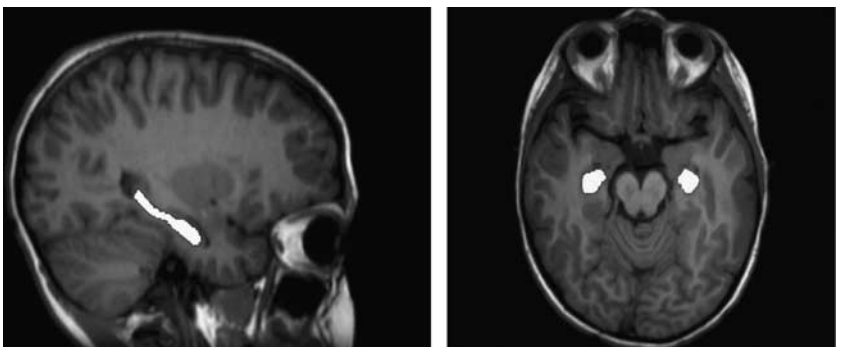
All participants underwent a 1-h structural MRI scan in the Diagnostic Imaging Unit at Sickkids, during which they viewed movies through MRI-compatible goggles. Structural MRI scans were obtained in a 1.5 T GE scanner (axial 3D FSPGR T1 IR prepared, TR = 10 ms, TE = 4.2 ms, TI = 400 ms, flip angle = 20°, FOV = 240 mm, acquisition matrix = 256 × 192, slice thickness = 1.5 mm, no gap; General Electric Canada, Mississauga, Ontario, Canada). Left and right hippocampal volumes were traced manually on a slice-by-slice basis (~80 tracings were hippocampus) using ANALYZE 9.0 software (Mayo Foundation, Rochester, Minnesota, USA). Designation of the hippocampal region included the cornu ammonis fields, the dentate gyrus, and the subiculum. Hippocampal boundaries were outlined from anterior to posterior in coronal images, such that the designation began at the rostral end where the hippocampal head first appeared below the amygdala and ended where the crura of the fornices departed from the hippocampal tail at the caudal end. A sample tracing is presented in Fig. 1. To reduce manual tracing errors, coronal images were magnified during tracing, and both sagittal and transverse images were used to verify hippocampal boundaries. A second trained image analyst traced 26% of right and left hippocampal volumes selected at random. Inter-rater reliability, as measured by Cronbach's α, was 0.94 and 0.93 for the left and right hippocampi. Total intracranial volume was determined using SPM5 (Wellcome Department of Imaging Neuroscience, UCL, London, UK). A neuroradiologist examined all MRI images for neuroradiological abnormalities and sent written reports to participants' family physicians.

Table 1 Demographic information

	CH-NoMus (*N*=14)	CH-Mus (*N*=11)	Con-NoMus (*N*=14)	Con-Mus (*N*=11)
Sex (number of females)	7	6	6	7
Age[a]	11.36 (1.50)	12 (1.41)	10.5 (0.65)	11.21 (1.67)
SES[a,b]	1.79 (0.87)	1.73 (0.65)	1.79 (0.80)	1.79 (0.89)
IQ[a]	106.82 (9.08)	106.36 (9.96)	118.64 (10.85)	113.21 (9.26)
Age when music lessons started[a]	NA	8.8 (3.12)	NA	8.25 (2.5)
Years of music lessons[a]	NA	3.2 (2.1)	NA	2.75 (2.4)
Music practice (min/week)[a]	NA	134.5 (101.4)	NA	75 (57.8)

CH, congenital hypothyroidism; Con, control; Mus, music; NA, not applicable; SES, socioeconomic status.
[a]Mean (SD).
[b]1 = high, 2 = medium–high, 3 = medium, 4 = medium–low income range.

Fig. 1



An example of a manual hippocampal tracing (white) in sagittal and axial views.

Data analysis

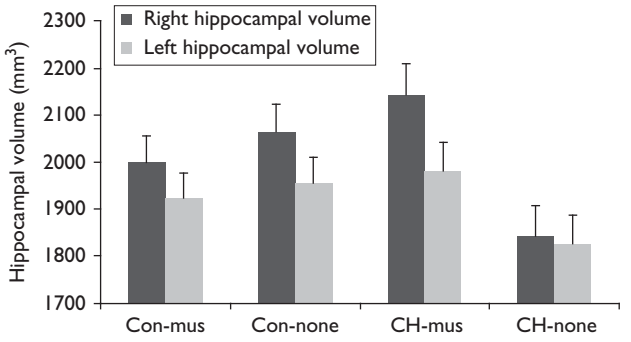
To determine whether our groups differed on demographics, we carried out a multivariate analysis of variance with group (CH/controls) and music lessons (yes/no) as between-participant factors and age, IQ, and SES as dependent measures. To determine whether the amount of music training was different between the CH and the control groups, we carried out a multivariate analysis of variance with group as a between-participant factor and age when music lessons started, years of music lessons, and minutes per week of music practice as dependent measures. To examine the effect of musical lessons on left and right hippocampal volumes, a multivariate analysis of covariance was used with group and musical lessons as between-participant factors and hippocampal hemisphere (left, right) as the dependent measure. To ensure that any structural differences found across groups were not confounded by brain size or demographic variables, we included intercranial volume, age, IQ, and SES as covariates.

Results

Demographic data are presented in Table 1. The control group was younger than the CH group [$F(1, 46) = 4.57$, $P = 0.04$] and had higher IQ scores [$F(1, 46) = 11.08$, $P = 0.002$]. Sex and SES did not differ between the four groups. Age when music lessons started, years of music lessons, and minutes per week of music practice did not differ between the CH-Mus and the Con-Mus groups (note: the large difference between the CH-Mus and Con-Mus for minutes per week of practice was driven by two outliers in the CH-Mus group).

A significant interaction between group and musical training was found for right hippocampal volumes [$F(1, 43) = 9.31$, $P = 0.004$] and a similar trend was found for left hippocampal volumes [$F(1, 43) = 2.72$, $P = 0.11$]. Post-hoc tests showed that CH participants without music lessons had smaller right hippocampal volumes than CH participants with music lessons [$t(20) = 4.11$, $P = 0.001$] and controls [$t(37) = 2.16$, $P = 0.04$ (Fig. 2)]. CH participants with music lessons had marginally larger right hippocampal volumes than controls with music lessons [$t(23) = 2.08$, $P = 0.05$], but did not differ from controls without music lessons. In controls, there was no difference in right hippocampal volumes between those with music lessons and those without [$t(26) = 0.45$, $P = 0.66$].

Fig. 2



Left and right hippocampal volumes in controls and children with CH, with and without music lessons. CH, congenital hypothyroidism; Con, control; mus, music.

Discussion

This study is the first to show that children with CH who received music lessons have larger right hippocampal volumes than those who did not receive music lessons. Importantly, the children with CH who received music lessons had comparable right hippocampal volumes to typically developing controls. Our findings suggest that music lessons may be a useful intervention for populations with abnormal hippocampal development, such as children with early TH deficiency [8]. Importantly, our results are consistent with other studies that have shown that musical training can induce both structural and functional neuroplasticity within the hippocampus as well as several other brain regions [12–14].

The specific influence of music training on the right hippocampus may reflect the function of this brain area. The right hippocampus is known to be associated with memory maintenance and recall related to spatial location [18–21]. Interestingly, spatial abilities have been shown to be enhanced after musical training [22,23] and in some situations, passive music listening has also been shown to have transient benefits on spatial abilities [24,25].

In the current study, we did not observe enhancements in hippocampal volume in typically developing children who received music lessons. This finding suggests that in healthy children, measureable neuroplastic changes in hippocampal structure may require many years of training and practice to become evident. Indeed, the neuroplastic effect of music lessons observed within our sample of children with CH suggests that when the hippocampus develops abnormally, it may be more susceptible to external factors, such as music lessons. Clearly, more research needs to be carried out to determine how musical training affects the functional properties of the hippocampus and to investigate how neuroplastic enhancement in the hippocampus in atypically developing children relates to performance on cognitive tasks.

Although the current study contributes considerably to our current understanding of the effects of music lessons on hippocampal structure in an atypically developing population, there are some important limitations to note. We are unable to make causal claims about the influence of music lessons on hippocampal volumes because those who took music lessons were self-selected (or parent-selected) and

not randomly assigned. The groups of children with and without music lessons were, however, similar on both SES and IQ. Moreover, the inclusion criterion for the music group (i.e. 1 year of lessons) was reasonably short; thus, children who stopped taking lessons for other factors were still included as having received music lessons. This is important because those children with CH who self-select (or parent-select) to cease music lessons (and will not become 'musicians') still showed a benefit compared with children with CH who never took music lessons. Accordingly, our results are highly suggestive that taking music lessons can ameliorate the influence of TH deficiency on hippocampal volume in children with CH. Future research with random assignment to a music lesson group could show causality.

Conclusion

Children with CH who have taken music lessons have normal hippocampal volumes. This suggests that hippocampal volume reductions in children with early TH deficiency may be ameliorated by music lessons during childhood. Our findings have implications for the management of CH and suggest that music lessons may be a beneficial intervention in populations with abnormal hippocampal development.

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Conflicts of interest

There are no conflicts of interest.

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