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Musical memory and hippocampus revisited: Evidence from a musical layperson with highly selective hippocampal damage

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ABSTRACT

The role of the human hippocampus for musical memory is still unclear. While imaging studies in healthy humans have repeatedly shown hippocampal activation in musical memory tasks, studies in musicians with chronic bilateral medial temporal lobe damage and in non-musicians suffering from neuro-degenerative diseases suggest that musical memory may at least partly be independent of hippocampal integrity. Here, we report on a musical layperson who acutely developed an amnesic syndrome in the context of autoimmune encephalitis. Structural and resting state functional MRI revealed exceptionally selective bilateral lesions of the hippocampi and altered functional connectivity with retrosplenial cortex and precuneus. Neuropsychological testing showed a severe global amnesic syndrome. Perception and processing of scales, melodic contours, intervals, rhythms and meter were unaffected. Most notably, the patient performed completely normally on tests of recognition memory for unfamiliar melodies and excerpts of complex musical material, while recognition memory for visual and verbal information was severely impaired. Likewise, emotional evaluation of musical excerpts did not differ from controls. We infer that integrity of musical processing and recognition memory in patients with hippocampal dysfunction does not result from training-induced or post-lesional brain plasticity, but rather reflects integrity of brain networks outside the hippocampi and presumably also outside retrosplenial cortex and precuneus. Our findings suggest major differences in the neural substrates of musical and non-musical recognition memory.

1. Introduction

Can the neural substrates of musical memory be dissociated from other memory domains? Following early reports of impaired musical memory in musical laypersons with temporal lobe damage (Samson & Zatorre, 1992; Squire, Schmolck, & Stark, 2001), case reports on amnesic musicians have shown that retention and acquisition of musical material can remain largely intact, even when recognition and recall in other memory domains is severely compromised (Cavaco, Feinstein, van Twillert, & Tranel, 2012; Finke, Esfahani, & Ploner, 2012; Valtonen, Gregory, Landau, & McCloskey, 2014). Most of these

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patients suffer from chronic bilateral extensive damage to medial temporal lobe subregions, i.e., to hippocampus, entorhinal cortex and adjacent cortex, suggesting that spared musical memory functions may depend on brain networks outside these regions (Cavaco et al., 2012; Finke et al., 2012; Valtonen et al., 2014). In support of this hypothesis, patients with mild cognitive impairment or dementia from Alzheimer's disease, i.e., disorders that affect medial temporal lobe regions early in the course of the disease, have repeatedly shown intact memory of famous tunes (Hsieh, Hornberger, Piguet, & Hodges, 2011; Jacobsen et al., 2015).

These clinical findings are not easy to reconcile with findings from functional imaging studies that repeatedly showed activation of the hippocampus during tasks that test recognition memory of melodies (Gagnepain et al., 2017; Watanabe, Yagishita, & Kikyo, 2008). Moreover, the hippocampus appears to be involved in encoding of musical stimuli during piano learning (Herholz, Coffey, Pantev, & Zatorre, 2016) and shows significant structural plasticity in response to professional musical training (Groussard et al., 2010; Herdener et al., 2010; Teki et al., 2012). In order to explain the inconsistencies between clinical and imaging findings, it has been claimed that various forms of musical memory exist that may be differentially affected by temporal lobe pathology (Baird & Samson, 2009, 2015). It is furthermore questionable, whether findings from professional musician patients allow for inferences on healthy brains of musical laypersons. There is ample evidence that early and extensive musical training induces structural and functional brain plasticity that facilitates the acquisition of new musical material and perhaps also of non-musical skills (Altenmüller & Furuya, 2016; Barrett, Ashley, Strait, & Kraus, 2013; Zatorre & Salimpoor, 2013). Case studies at least suggest that these changes may also facilitate recovery from temporal lobe damage (Galarza et al., 2014; Trujillo-Pozo, Martín-Monzón, & Rodríguez-Romero, 2013). Because of such post-lesional adaptive changes, it is generally not clear whether differential impairments of distinct memory domains in patients with chronic brain lesions also result from differential efficiency of reorganisation (Esfahani-Bayerl et al., 2016). Lastly, the underlying disorders in most patients such as herpes encephalitis, global cerebral hypoxia or neurodegeneration are mostly not selective and only rarely allow for clear-cut brain-behavior correlations, in particular for the hippocampus.

In the present study, we took the unique opportunity to study musical memory in a musical layperson with acute and exceptionally selective bilateral lesions of the hippocampus. Despite a severe and global amnesic syndrome, the patient performed completely normally in tests of recognition memory for music, while recognition memory for visual and verbal information was severely impaired. We infer that encoding, maintenance and retrieval of new musical material can efficiently be mediated by networks outside the hippocampus.

2. Material and methods

2.1. Study outline

We report on a young male who acutely developed a selective bi-hippocampal syndrome. In addition to extensive testing with established neuropsychological tasks and testing of basic music abilities, we investigated his musical and non-musical recognition memory with tasks that we had developed previously in work with an amnesic professional musician with more extensive bilateral temporal lobe damage (Finke et al., 2012). Patient's performance was compared to a group of healthy controls. Informed consent was obtained from all subjects before participation in the study, which was approved by the local Ethical Committee and conducted in conformity with the Declaration of Helsinki. No part of the study procedures or analyses was pre-registered prior to the research. Control sample size was estimated prior to analysis based on data from a previous case study (Finke et al., 2012). No data were excluded. All manipulations and measures of the study are reported.

2.2. Subjects

2.2.1. Patient with bilateral hippocampal lesions

A 26-year-old man presented with a one-week history of malaise and progressive confusion to our emergency room. On admission, the patient was alert and cooperative, but fully disoriented and showed a severe and global amnesic syndrome. He was neither able to report biographical details about the weeks and months preceding admission, nor did he retain any information about his current situation, e.g., the name of the hospital, the faces and names of caregivers, the layout of the ward, contents of meals or information about his medical condition. The patient was afebrile, results of general physical and neurological examination were completely normal. Apart from insulin-dependent diabetes mellitus, his medical history revealed no further disorders. His education consisted of twelve years school and four years university, where he had obtained a bachelor's degree in history and literature. He had played the violin for several years during late childhood and adolescence and stopped playing regularly at the age of 16. He was still able to read notes but was not able to sight-read or write music although he had received some training in sight-reading in his youth. He only had some rudimentary knowledge of music theory. Cranial MRI on admission showed a hyperintense signal in both medial temporal lobes (Fig. 1).

In T2-and FLAIR-weighted images, this hyperintensity affected the entire rostrocaudal extent of the hippocampus bilaterally, but spared amygdala, entorhinal cortex, perirhinal cortex and parahippocampal cortex. Diffusion-weighted images showed restricted diffusion in both hippocampi. No gadolinium enhancement and no further brain lesions were found. Routine laboratory tests were normal. CSF showed elevated protein (1082 mg/l), but no cells, no oligoclonal bands and normal lactate levels. Extensive investigations for viral and bacterial infections in serum and CSF were negative. Testing for onconeural antibodies and antibodies involved in autoimmune encephalitis was negative in serum and CSF (including anti-NMDA receptor, -LGI1, -VGKC complex, -CASPR2, -AMPA receptor, -$GABA_B$-receptor, -D2-receptor, -DPPX, -GAD, -Glycine-receptor, -Hu, -Ri, -CV2/-CRMP5, -Ma2/Ta, -Amphiphysin, -Tr, -GAD65). Screening for neoplastic diseases was negative. Resting state fMRI showed reduced functional connectivity of the right and left hippocampi with bilateral retrosplenial cortex and precuneus (Fig. 2).

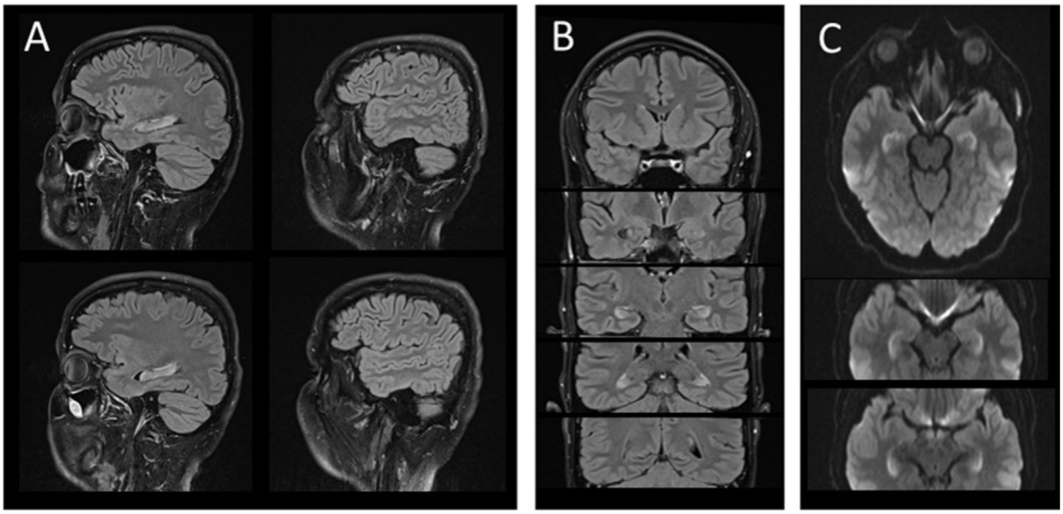

Fig. 1 – Structural MRI. A) FLAIR-weighted sagittal sections at the level of the hippocampus. Top row, left hemisphere; bottom row, right hemisphere. B) FLAIR-weighted coronal sections arranged from rostral (top) to caudal (bottom). C) Diffusion-weighted axial images arranged from dorsal (top) to ventral (bottom). Note hyperintense signal of the entire rostrocaudal extent of the hippocampus bilaterally and sparing of amygdala and immediately adjacent cortex.

Due to the clinical features and the pattern of structural and functional MRI abnormalities, a diagnosis of antibody-negative autoimmune-encephalitis was made and treatment with five days of methylprednisolone (1000 mg/d i.v.) and five cycles of plasmapheresis was initiated. Repeat MRI twelve days after admission showed partial remission of hippocampal hyperintensities.

On neuropsychological testing, the patient was fully compliant and emotionally appropriate. Consistent with the patient's high educational level (16 years), all measures of intelligence, alertness, attention, working memory, visuo-perceptive and visuo-constructive abilities were above average or within the normal range. However, both verbal and visuo-spatial memory were severely impaired. When tested with the VLMT (Verbaler Lern-und Merkfähigkeitstest, a German Variant of the Rey Auditory Verbal Learning Test, RAVLT; Helmstaedter, Lendt, & Lux, 2001), the patient showed an almost absent delayed recall and severely impaired recognition of word lists (Table 1, Fig. 3).

Likewise, on testing with the Rey–Osterrieth Complex Figure Test (ROCF), he was severely impaired in immediate and delayed recall, while he was not impaired in copying the figure (Table 1).

2.2.2. *Healthy controls*

The control group consisted of 14 subjects without any history of neurological or psychiatric disorders (5 female, 9 male, mean age 31.3 ± 3.2 years, $p = .68$ difference with patient; mean educational level 17.2 ± .5 years, $p = .57$ difference with patient). None of the controls was an expert musician. None of controls performed music regularly or played a musical instrument on a daily basis. However, most subjects met Grison's fourth level of musical culture (Grison, 1972), and were able to play an instrument, but were not taught in musical theory or sight-reading (patient, 5; controls 4.1 ± .3; $p = .429$ difference).

2.3. *Tasks and procedures*

2.3.1. *Basic musical abilities*

Perception and processing of music was examined with the Montreal Battery for Evaluation of Amusia (‘MBEA’), i.e., the most widely used battery of tests for detection of musical disorders (Peretz, Champod, & Hyde, 2003). Six subtests assess perception of scales, melodic contours, intervals, rhythms and meter and incidental encoding of melodies.

2.3.2. *Musical memory task*

We used a variant of a musical memory task, which had been developed in a previous case study of musical memory in an amnesic musician (Finke et al., 2012). Stimuli consisted of 20 musical excerpts with a length of 15–30 sec. Every excerpt consisted of instrumental music, which had been composed recently. None of the excerpts was associated with any lyrics. Stimuli always contained the main theme of the piece. None of the excerpts was familiar to any participant. Following presentation of the excerpt, subjects were requested to assign the excerpt to one out of five emotional categories: joyful, thrilling/threatening, sad/melancholic, solemn/ceremonial and peaceful. In preceding pilot experiments on 35 subjects (19 males, 16 females, mean age 39.5 ± 2.43 ys), we had ensured unambiguity of emotional categorization with an average agreement of 94.6% across excerpts. Ninety minutes after stimulus presentation and emotional characterization, subjects received a surprise memory test, where each of the evaluated excerpts was presented with a new musical excerpt, which had been matched to the probe excerpt in terms of instrumentation, mood and musical character. Stimulus selection was supervised and approved by two professional musicians. Subjects were requested to identify the excerpt that had been presented previously. Memory performance was expressed in percent correct responses. In addition, we quantified emotional categorization of excerpts by calculating the percentage of responses that deviated from the

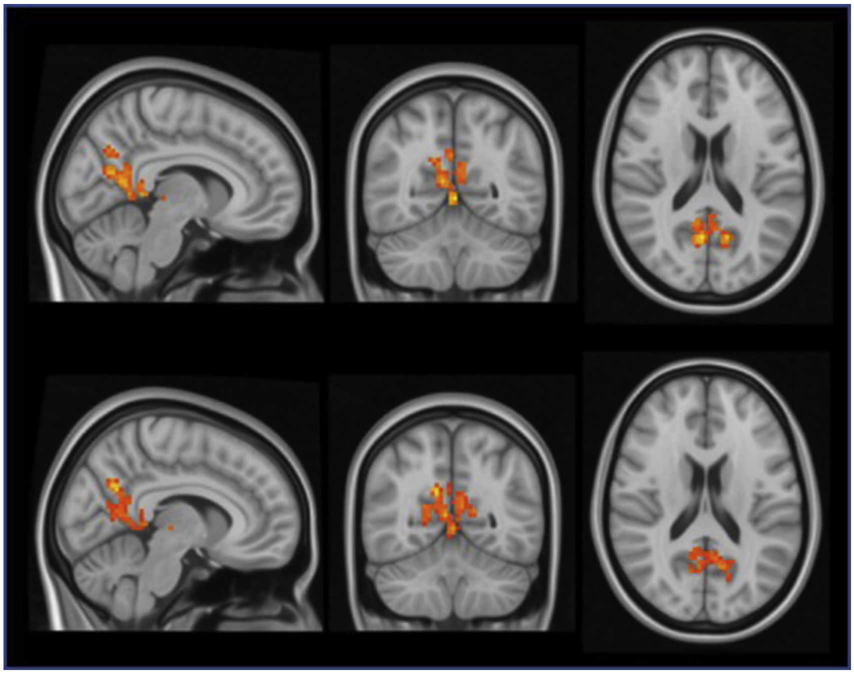

Fig. 2 – Resting state functional MRI. Network effects of hippocampal dysfunction. Note altered functional connectivity of the left hippocampus (top) and the right hippocampus (bottom) with retrosplenial cortex and precuneus. Functional connectivity analyses were performed using a seed–based correlation analysis with left and right hippocampus as regions-of-interest and using FSL tools (www.fmrib.ox.ac.uk). After pre-processing, average time series from each hippocampus were correlated with the time series of every voxel in the brain, followed by a normalization of the resultant individual whole–brain correlation maps using Fisher's r-to-z transformation. Group-level comparisons between the patient and 20 age-matched healthy controls were carried out using FSL FLAME and corrected for multiple comparisons (cluster-forming threshold $z > 2.3$, corrected cluster significance threshold $p < .05$). See https://osf.io/3ndxg/ for analysis codes and group z maps of resting state analysis. The ethical requirement to ensure participant confidentiality precludes open access to potentially identifiable individual MRI data. Furthermore, the conditions of our ethics approval do not cover public archiving of anonymised individual MRI data. Readers seeking access to the data should contact authors CJP, CF or send a formal request directly to the ethics committee of the Charité – Universitätsmedizin Berlin.

average categorization of the control group. Legal copyright restrictions do not permit us to publicly archive the full set of stimuli used in this task. Readers seek access to the stimuli are referred to https://osf.io/3ndxg/for further details and are advised to contact author CJP.

2.3.3. *Face memory task*

Twenty pictures of unfamiliar male faces taken from a public database were presented successively for 15 sec each (Finke et al., 2012). Subjects were requested to rate the trustworthiness of each face. After 90 minutes, subjects received a surprise memory test, where the 20 probe faces which had been rated, were presented pairwise with new faces, which had been matched to the probe faces in terms of age, hairstyle and clothing. Subjects were requested to identify the probe faces. Legal copyright restrictions do not permit us to publicly archive the full set of stimuli used in this task. Readers seek access to the stimuli are referred to https://osf.io/3ndxg/for further details and are advised to contact author CJP.

2.3.4. *Object memory task*

Eighteen unfamiliar drawings of animals taken from children's memory games were presented for 15 sec each (Finke et al., 2012). Subjects were requested to determine the predominant color of the drawings. After 90 minutes, subjects received a surprise memory test, where the probe drawings were

Table 1 – Visual and verbal memory performance in patient and controls (n = 14). Control values are means ± standard errors; ROCF, Rey–Osterrieth Complex Figure Test; VLMT, Verbaler Lern-und Merkfähigkeits-Test, a German Variant of the Rey Auditory Verbal Learning Test. Statistical testing was done by using a Bayesian approach (Crawford et al., 2010, 2011).

Group	ROCF (%)			VLMT (%)		
	Copy	Immediate	Delay	List 6	Recall	Recognition
Patient	100	19	0	33	0	53 (8 false positives)
Controls	99.8 ± .2	85.3 ± 1.7	84.5 ± 1.8	95.2 ± 1.3	96.2 ± 1.3	99.5 ± .5
p-value	.79962	<.0001	<.0001	<.0001	<.0001	<.0001

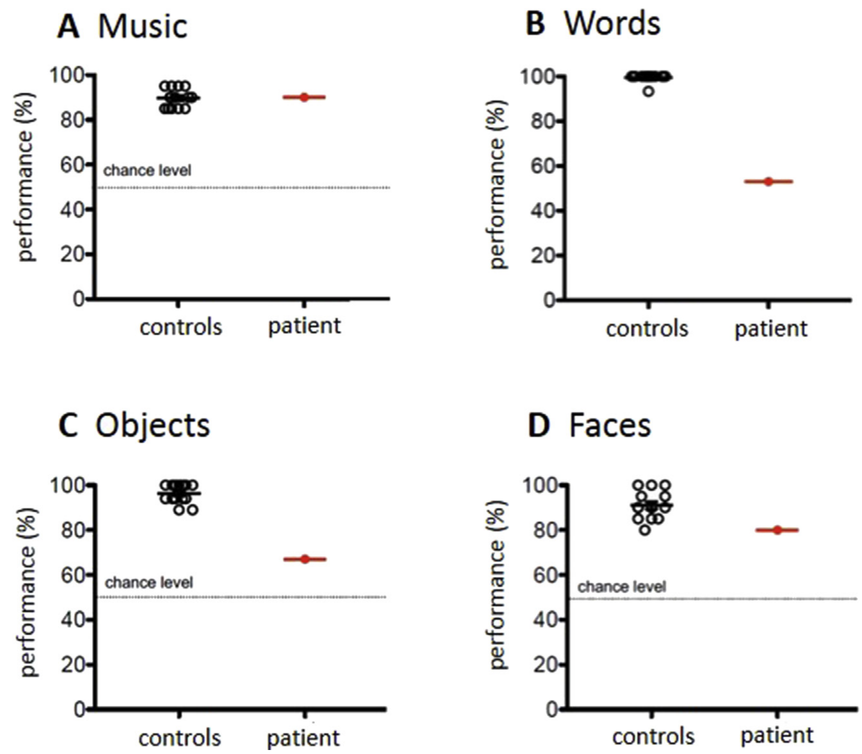

Fig. 3 — Results of four recognition memory tests. Black circles, controls (n = 14); red dot, patient. A) Musical memory as assessed with a forced choice recognition test for excerpts of instrumental music. B) Word recognition as assessed with the VLMT, a German Equivalent of the Rey Auditory Verbal Learning Test. C) Memory for visual objects as assessed with a forced choice recognition test for animal drawings. D) Memory for faces as assessed with a forced choice recognition test for faces. Note normal performance in A, severe impairment in B and C, and inferior performance in D. See text for statistics.

presented pairwise with new drawings, which had been matched to the probe drawings in terms of color, content and artistic character. Subjects were requested to identify the probe drawing. Legal copyright restrictions do not permit us to publicly archive the full set of stimuli used in this task. Readers seek access to the stimuli are referred to https://osf.io/3ndxg/ for further details and are advised to contact author CJP.

Cognitive testing of our patient was performed on days three and four following admission. The tests were presented in the same order to the patient and to the controls. Testing started with evaluation of the emotional categorization of musical excerpts. During the 90-minute delay that preceded recognition memory testing, subjects performed the incidental encoding part of the face and object recognition memory tasks. Thus, by the time of music recognition memory testing, encoding of the other memoranda was already completed.

2.4. *Data analysis*

Group averages are reported as means with standard errors throughout. Statistical comparisons between patient and control group were conducted by using a Bayesian approach for comparison of a single case score to scores obtained in a control sample as proposed by Crawford and Garthwaite (Crawford et al., 2010; Crawford, Garthwaite, & Ryan, 2011; http://homepages.abdn.ac.uk/j.crawford/pages/dept/Single_Case_Effect_Sizes.htm). All behavioral data for these analyses is publicly archived under https://osf.io/3ndxg/.

3. Results

3.1. *Basic musical abilities*

Testing with the MBEA revealed that our patient's ability to perceive, process and differentiate tonal scales, melodic contours, intervals, rhythms and meters was completely intact. Performance in each of the corresponding MBEA subtests was ≥27/30 correct responses, which is consistent with the mean of the normal sample in the original paper of Peretz and colleagues (27/30 correct responses in 160 subjects, Peretz et al., 2003). Likewise, as in our previous report on an amnesic musician (Finke et al., 2012), this patient's ability to recognize previously presented melodies of the MBEA during an incidental memory test at the end of the testing session was entirely normal. His recognition of the brief melodic piano sequences (≤6.4 s) was even above the control average (29/30 correct responses).

3.2. *Recognition memory for music, faces and objects*

In the musical recognition memory test, during emotional evaluation of more complex musical stimuli, his ratings of the unfamiliar musical excerpts did not differ from controls (patient, 85%; controls 83.9 ± 1.7%; $p = .871$). Although he completely forgot the fact that he had rated the musical excerpts 90 minutes prior to incidental memory testing, he showed a clear preference for previously presented musical excerpts and normal recognition memory performance (patient, 90%; controls 89.6 ± 1.1%; $p = .934$; Fig. 3).

It is very unlikely that this finding simply reflected retrieval of musical material that had successfully consolidated prior to his illness, since all musical excerpts had been taken from contemporary compositions that were rated as 'completely unfamiliar' by normal subjects.

Theoretically, integrity of musical recognition memory in our patient may be due to the fact that non-verbal recognition memory is generally less-dependant on the hippocampus than recall (see Brown, Warburton, & Aggleton, 2010; H. Eichenbaum, Yonelinas, & Ranganath, 2007; Squire & Wixted, 2011 for discussion). Indeed, recognition of newly learned faces was below control average, yet not significantly different from controls (patient, 80%; controls 91.1 ± 1.7%; $p = .111$; Fig. 3). Further testing of non-verbal recognition memory however argues against a pure recognition-recall dissociation that accounts for the findings in our patient. Similar to his performance in the two recall conditions of the ROCF task, our patient's performance in visual object recognition memory fell far below the control group (patient, 67%; controls 96.3 ± 1.1%; $p = .0001$; Fig. 3).

4. Discussion

The present study reports the neuropsychological and imaging findings in a young patient with an acute amnesic syndrome and highly selective bilateral hippocampal lesions. Despite a severe impairment in most memory modalities, the patient performed normally in recognition memory of unfamiliar musical material. We will discuss how these findings contribute to current research on brain networks that support processing and memory of music.

The role of the hippocampal formation for musical memory is still a matter of debate. Early case series with musical laypersons suffering from various disorders affecting the hippocampus and adjacent regions have shown impaired recognition memory for unfamiliar melodies (Samson & Zatorre, 1992; Squire et al., 2001). Subsequent case reports in professional and amateur musicians with amnesic syndromes have reported surprisingly well-preserved musical memory despite extensive bilateral damage to medial temporal lobe structures (Cavaco et al., 2012; Finke et al., 2012; Valtonen et al., 2014). While these latter reports are fascinating case histories, their significance for a better understanding of representation of music in the normal brain is not unequivocal. Studies in professional musicians have shown that life-long musical training induces significant brain plasticity that may facilitate musical memory and non-musical cognitive functions (Altenmüller & Furuya, 2016; Barrett et al., 2013; Herholz & Zatorre, 2012; Schlaug, 2015). These networks for musical processing and memory likely involve several temporal neocortical regions such as superior and inferior temporal gyrus and sulcus as well as prefrontal and parietal cortex (Koelsch, 2014; Peretz & Zatorre, 2005; Rauschecker, 2014). In addition, preserved musical memory in musician patients could also reflect integrity of neocortex involved in musical memory (Finke et al., 2012; Valtonen et al., 2014). An important potential source of inconsistencies between patient studies is the heterogeneity of disorders and the variable patterns of damage to hippocampus and extra-hippocampal temporal cortex in earlier studies of musical recognition memory (e.g., in Samson & Zatorre, 1992; Squire et al., 2001) Comparison of memory performance in patients with different disorders affecting the hippocampus suggests that these hippocampal/extra-hippocampal lesion patterns are significantly dependent on lesion etiology (Esfahani-Bayerl et al., 2016). It is moreover unclear whether the resulting deficits in musical memory are indeed specific to music or result from a more global deficit in auditory memory, as most studies did not control for non-musical meaningful sounds (Lancelot et al., 2003). Our case study addresses these open issues in several respects: First, our patient's musical practice did not transcend a few years of violin training on a "hobby"-level during youth. Significant training-induced plasticity is therefore unlikely to account for his preserved musical memory. Second, our patient showed a bilateral hippocampal lesion of exceptional selectivity. Structural MRI as well as neuropsychological testing yielded no evidence for damage of further brain regions outside the hippocampi. Conversely, while it cannot be excluded that some residual hippocampal function may have contributed to preservation of musical memory in our patient, the severity of his amnesic syndrome and the bilateral rostro-caudal extent of his lesions argue strongly against incomplete hippocampal damage as a major explanation for our findings. Third, we investigated our patient during the acute stage of his amnesic syndrome. Compensatory processes that may have differentially acted on distinct memory domains are very unlikely. We are thus confident that our patient's remarkable integrity of musical memory is best explained by a partial independence of networks for musical recognition memory from the hippocampus.

On the first glance, our results seem to support fMRI and PET studies of musical memory that reported temporal neocortical and inferior frontal activation during recognition memory tests of melodies in musical laypersons but did not find activation of the hippocampus (Groussard, Rauchs, et al., 2010; M; Groussard, Viader, et al., 2010; Herholz & Zatorre, 2012). However, these studies focussed on highly popular musical material that was already familiar to most study participants prior to the experiments and that may therefore have been consolidated and re-consolidated for years. Although it is largely unknown how musical memory develops across time, it appears that consolidation may render representation of melodic information progressively independent from the hippocampus – as suggested by the 'standard' model of memory consolidation (Squire, Genzel, Wixted, & Morris, 2015). Consistent with this hypothesis, PET imaging during learning of newly composed musical phrases in laypersons yielded right hippocampal and inferior frontal activation (Watanabe et al., 2008). Several subsequent fMRI studies found hippocampal activation in relation to several further aspects of musical processing, such as processing of music-evoked emotions (Koelsch, 2014), binding of lyrics to familiar melodies (Alonso et al., 2016), and the feeling of familiarity, when musical stimuli are selected according to participants individual musical experience (Plailly et al., 2007).

In addition to hippocampal activation in functional imaging studies of musical laypersons, studies in professional musicians have shown that the hippocampus shows significant plasticity in relation to musical training, with enhanced neural responses to temporal novelty in the auditory domain – presumably reflecting a tuning of aural skills during musical education (Herdener et al., 2010). The structural and functional differences between the hippocampi of musicians and non-musicians have further been speculated to correlate with the development of specific musical memory abilities in musicians, where familiar melodies are associated with an increased number of episodic memories in comparison to non-musicians (M. Groussard et al., 2010). A similar hypothesis has been put forward in a study of piano tuners that showed increased grey matter volume in anterior hippocampus and white matter volume in the posterior hippocampus as a function of years of tuning experience (Teki et al., 2012). It has been suggested that these changes result from establishment and consolidation of memory of specific beat-rate templates for tonal intervals. In line with these findings, it has been shown that familiarity decisions on musical excerpts are faster in musicians compared to controls. The increase in speed correlated with an increase in activation of the left hippocampus that in turn resulted from increased top-down excitatory signals from inferior frontal cortex (Gagnepain et al., 2017).

How do the findings in our patient relate to these imaging results? The complete intactness of our patient's musical recognition memory seems to be at odds with those studies that reported activation or plasticity of the hippocampus in relation to musical memory demands in normal subjects. While our patient was undoubtedly able to encode, maintain and retrieve the unfamiliar musical excerpts of our task like healthy controls, this does not necessarily mean that the hippocampus is not involved in musical memory. Performance of controls was close to ceiling. It appears therefore possible that an increase in task difficulty or memory delay would have revealed deficits that went undetected in our comparatively simple task. Moreover, it has been speculated previously that musical practice in general and learning of musical material in particular is associated to learning of a multitude of contextual and autobiographical details that may drive hippocampal activation in fMRI studies and hippocampal plasticity in musicians (Gagnepain et al., 2017; Groussard et al., 2010). Musical recognition memory tests may thus induce the formation of collateral episodic musical memories, even if a simple ‘yes-no’ behavioral readout does not depend on them. Due to the limitations inherent in an acute clinical setting, we were not able to further investigate the possibility of an episodic musical memory deficit in our patient. However, we can nevertheless make an important general point about the neural substrates of memory. According to dual process models of memory, recognition is thought to be supported by two sub-processes, familiarity and recollection (Mandler, 1980). There has been an intense debate about whether these two sub-processes both depend on the hippocampus or whether there are distinct contributions of hippocampus, perirhinal cortex and parahippocampal cortex (Brown et al., 2010; Eichenbaum et al., 2007; Squire & Wixted, 2011). Although we have no data on episodic recollection of musical memoranda in our patient, it is obvious that dependency of both sub-processes on the hippocampus is not compatible with our results. Rather, they support the hypothesis that familiarity-based recognition – at least of music – is mainly mediated by brain regions outside the hippocampus. The simultaneous impairment in recognition of visual and verbal information in our patient however suggests that this dissociation does not equally apply to other memory domains. Consistent with this interpretation, comparison of hippocampal activation during musical and verbal recognition memory indeed showed differential recruitment of the hippocampus (Groussard, Rauchs, et al., 2010; Groussard, Viader, et al., 2010).

Despite the exceptional selectivity of our patient's lesion, resting state fMRI demonstrated significant network effects outside the hippocampus. We found alterations of functional connectivity of both hippocampi with retrosplenial cortex and precuneus. While retrosplenial activation has not been reported in studies of musical memory so far, the precuneus was activated in several fMRI studies of musical memory (Herholz & Zatorre, 2012; Plailly et al., 2007; Satoh, Takeda, Nagata, Shimosegawa, & Kuzuhara, 2006; Watanabe, Savion-Lemieux, & Penhune, 2007). In musicians, this region also shows increased functional connectivity with regions outside the default mode network related to auditory and emotional processing (Tanaka & Kirino, 2016). It is currently not clear, what the role of restrosplenial cortex and precuneus for musical memory might be. Evidence from imaging and human lesion studies however implicates the precuneus in encoding and retrieval of several non-musical memory domains (Gilmore, Nelson, & McDermott, 2015) and retrosplenial cortex in spatial navigation and episodic memory with a particular role for consolidation and retrieval of contextual information (Ranganath & Ritchey, 2012; Vann, Aggleton, & Maguire, 2009). These data thus lend further support to the idea that musical recognition memory is a cognitive faculty that operates largely independent of networks that are involved in other memory domains. It will be important to investigate whether these regions are involved in recollection of episodic information during learning of musical material.

With respect to basic musical abilities, we found no detectable abnormalities in processing and recognition of scales, melodic contours, intervals, rhythms and meter when the patient was tested with an established battery for evaluation of musical disorders. These findings fit the observation of unimpaired perception, encoding, working memory and retrieval of auditory information (including unfamiliar melodies) in earlier studies of patients with more extensive temporal lobe damage (Squire et al., 2001). While these results do not exclude that more demanding behavioral contexts, like those that occur during active music-making, would ultimately have revealed deficits in musical abilities, most of the musical processing assessed by the MBEA appeared not to depend on hippocampal integrity. We thus deem it likely that deficient MBEA performance following acute brain lesions that include the medial temporal lobe does not reflect hippocampal dysfunction per se, but rather other lesion-associated factors, e.g., damage to long-range white matter pathways – as has been speculated recently (Sihvonen, Ripollés, Rodríguez-Fornells, Soinila, & Särkämö, 2017). Likewise, and to our surprise, evaluation of the emotional character of musical excerpts did not differ from controls although evidence implicates the anterior hippocampus in emotional processing of music (Koelsch, 2014). It appears thus possible, that emotional evaluation was performed with a "cognitive" strategy that mainly relied on recognition of typical rhythmic, harmonic and melodic signatures of a distinct emotional content rather than on reporting of the patient's emotional reactions.

5. Conclusions

Taken together, our findings add clarity to the role of the hippocampus in processing and memory of music. They show that basic musical abilities and musical recognition memory can be intact despite acute and bilateral hippocampal lesions with concomitant deficits in non-musical recognition memory. Previous reports of intact musical recognition memory in musician and non-musician patients with less selective hippocampal damage or neurodegenerative diseases are therefore likely to reflect organization of networks for musical memory that differ considerably from those involved in other memory domains, including verbal memory. Conversely, impaired recognition memory for music in studies of patients with lesions of the temporal lobe likely reflects damage to these networks rather than to the hippocampus. Preserved recognition of music is a major prerequisite for the experience of pleasure during music listening (van den Bosch, Salimpoor, & Zatorre, 2013) and for music-based neurological rehabilitation (Sihvonen, Särkämö, et al., 2017). However, full musical experience also depends on linking melodies with episodic and contextual information. It will thus be important to study how hippocampal dysfunction affects this aspect of musical memory.

CRediT authorship contribution statement

Nazli Esfahani-Bayerl: Investigation, Methodology, Resources, Formal analysis, Data curation, Visualization, Writing - original draft. **Carsten Finke:** Investigation, Methodology, Resources, Formal analysis, Data curation, Visualization, Writing - review & editing. **Ute Kopp:** Investigation, Writing - review & editing. **Daa-Un Moon:** Investigation. **Christoph J. Ploner:** Conceptualization, Investigation, Methodology, Validation, Visualization, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration.

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