

Why musical memory can be preserved in advanced Alzheimer's disease

Jörn-Henrik Jacobsen,^{1,2} Johannes Stelzer,^{1,3,4} Thomas Hans Fritz,^{1,5,6} Gael Chételat,^{7,8,9,10} Renaud La Joie^{7,8,9,10} and Robert Turner¹

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Musical memory is considered to be partly independent from other memory systems. In Alzheimer's disease and different types of dementia, musical memory is surprisingly robust, and likewise for brain lesions affecting other kinds of memory. However, the mechanisms and neural substrates of musical memory remain poorly understood. In a group of 32 normal young human subjects (16 male and 16 female, mean age of 28.0 ± 2.2 years), we performed a 7 T functional magnetic resonance imaging study of brain responses to music excerpts that were unknown, recently known (heard an hour before scanning), and long-known. We used multivariate pattern classification to identify brain regions that encode long-term musical memory. The results showed a crucial role for the caudal anterior cingulate and the ventral pre-supplementary motor area in the neural encoding of long-known as compared with recently known and unknown music. In the second part of the study, we analysed data of three essential Alzheimer's disease biomarkers in a region of interest derived from our musical memory findings (caudal anterior cingulate cortex and ventral pre-supplementary motor area) in 20 patients with Alzheimer's disease (10 male and 10 female, mean age of 68.9 ± 9.0 years) and 34 healthy control subjects (14 male and 20 female, mean age of 68.1 ± 7.2 years). Interestingly, the regions identified to encode musical memory corresponded to areas that showed substantially minimal cortical atrophy (as measured with magnetic resonance imaging), and minimal disruption of glucose-metabolism (as measured with ^{18}F -fluorodeoxyglucose positron emission tomography), as compared to the rest of the brain. However, amyloid- β deposition (as measured with ^{18}F -flobetapir positron emission tomography) within the currently observed regions of interest was not substantially less than in the rest of the brain, which suggests that the regions of interest were still in a very early stage of the expected course of biomarker development in these regions (amyloid accumulation \rightarrow hypometabolism \rightarrow cortical atrophy) and therefore relatively well preserved. Given the observed overlap of musical memory regions with areas that are relatively spared in Alzheimer's disease, the current findings may thus explain the surprising preservation of musical memory in this neurodegenerative disease.

- 1 Max Planck Institute for Human Cognitive and Brain Sciences, 04103 Leipzig, Germany
- 2 ISLA, Informatics Institute, University of Amsterdam, 1098XH Amsterdam, The Netherlands
- 3 Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Hvidovre, 2650 Hvidovre, Denmark
- 4 Max Planck Institute for Biological Cybernetics, 72076 Tuebingen, Germany
- 5 Department of Nuclear Medicine University of Leipzig, Liebigstrasse 18, 04103 Leipzig, Germany
- 6 Institute for Psychoacoustics and Electronic Music (IPEM), Blandijnberg 2, B-9000 Ghent, Belgium
- 7 INSERM, U1077, Caen, France
- 8 Université de Caen Basse-Normandie, UMR-S1077, Caen, France
- 9 Ecole Pratique des Hautes Etudes, UMR-S1077, Caen, France
- 10 CHU de Caen, U1077 Caen, France

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Correspondence to: Jörn-Henrik Jacobsen,
Intelligent Systems Lab,
Informatics Institute,
University of Amsterdam,
Science Park 904,
1098 XH Amsterdam,
The Netherlands
E-mail: mail@henrik-jacobsen.com

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Abbreviations: FDG= ^{18}F -fluorodeoxyglucose; MVPA=multivariate pattern analysis; SMA = supplementary motor area

Introduction

Musical memory entails the neural encoding of musical experiences. The relevant neuronal substrates have long been the object of research enquiry. In his seminal studies stimulating the cortex with electrodes, Wilder Penfield was the first to describe a possible role of the temporal cortex in the encoding of (episodic) musical memory (Penfield and Perot, 1963). Several more recent lesion studies support the hypothesis that temporal lobes are included in a musical memory network (Samson and Zatorre, 1991; Peretz, 1996; Samson and Peretz, 2005). However, musical memory seems not to rely solely on temporal lobe networks, a conclusion supported by evidence that recognition of a musical piece by a patient with bilateral temporal lobe lesion was enhanced by repeated exposure (Samson and Peretz, 2005).

It is likely that neural encoding of musical experiences is accomplished by more than one brain network (Baird and Samson, 2009). Attempts are often made to characterize musical memory in terms of established memory categories such as episodic/semantic, short-term/long-term, implicit/explicit, which are generally considered to be supported by different anatomical brain networks. For example it has been shown in a PET study that the underlying brain processes differ for semantic and episodic memory aspects of music, suggesting that they are based on two distinct neural networks (Platel *et al.*, 2003). The anatomy of episodic musical memory has further been studied in a functional MRI experiment, using autobiographically relevant long-known musical pieces, which showed a crucial role for medial prefrontal and lateral prefrontal cortex, and for areas within the superior temporal sulcus and superior temporal gyrus (Janata, 2009). Several studies have investigated recognition (semantic) and recollection (episodic) during music presentation, finding distributed task involvement in temporal, prefrontal and auditory cortex. Musical memory clearly has many related aspects. Different types of music-related memory appear to involve different brain regions, for instance when lyrics of a song are remembered, or autobiographical events are recalled associated with a particular piece of music (Zatorre *et al.*, 1996; Halpern and Zatorre,

1999; Platel *et al.*, 2003; Satoh *et al.*, 2006; Plailly *et al.*, 2007; Watanabe *et al.*, 2008; Brattico *et al.*, 2011). The experimental design of the present study is intended to provide averaging over particular musical associations, to provide a simple comparison between unknown, recently-heard and long-known musical passages.

Musical memory is specific and task-dependent

Musical memory may rely on distinct and task-dependent memory systems. It has been shown that memory for music can be severely damaged while other memory systems remain mostly unimpaired (Peretz, 1996). Conversely, musical memory was found to be preserved in severely amnesic patients with vast lesions of the right medial temporal lobe, the left temporal lobe and parts of left frontal and insular cortex, with similar findings in patients with bilateral temporal lobe damage (Eustache *et al.*, 1990; McChesney-Atkins *et al.*, 2003; Samson and Peretz, 2005; Finke *et al.*, 2012). This strongly suggests that the network encoding musical memory is at least partly independent of other memory systems. Interestingly, it has been shown that different aspects of musical memory can remain intact while brain anatomy and corresponding cognitive functions are massively impaired (Baird and Samson, 2009; Finke *et al.*, 2012).

Musical memory also appears to represent a special case in Alzheimer's disease, in that it is often surprisingly well preserved (Vanstone and Cuddy, 2010), especially implicit musical memory, which may be spared until very late stages of the disease. Because these findings are mainly derived from case studies, it is not clear under what circumstances which aspect of musical memory is preserved (Baird and Samson, 2009; Johnson *et al.*, 2011). Baird and Samson (2009) have indeed proposed that this preserved memory for music may be due to intact functioning of brain regions that are relatively spared in Alzheimer's disease. However, this hypothesis has not yet received experimental support.

Anatomy of Alzheimer's disease progression

In the early stages of Alzheimer's disease, structural impairment typically develops along the hippocampal pathway (entorhinal cortex, hippocampus and posterior cingulate cortex) (Frisoni *et al.*, 2010). Early degeneration is found mainly in the temporal and parietal lobes, the orbitofrontal cortex, the precuneus and in other large neocortical areas, while to a large degree the primary sensory, motor, visual, and anterior cingulate cortices are spared (Hoesen *et al.*, 2000; Thompson *et al.*, 2003, 2007; Singh *et al.*, 2006; Frisoni *et al.*, 2007, 2010; Cuingnet *et al.*, 2011; Villain *et al.*, 2012; Lehmann *et al.*, 2013). *In vivo* imaging of Alzheimer's disease progression uses biomarkers to track anatomical changes in the human cortex. According to the amyloid cascade hypothesis, a disruption of balance between production and clearance of amyloid precursor protein leads to formation of amyloid- β plaques, development of neurofibrillary tangles, neural dysfunction, regional atrophy and finally dementia (Hardy and Higgins, 1992; Benzinger *et al.*, 2013). Thus different *in vivo* imaging modalities are utilized to investigate amyloid- β deposition (^{18}F -florbetapir PET), glucose hypometabolism [^{18}F -fluorodeoxyglucose (FDG) PET] and cortical atrophy (structural MRI), which are all hallmarks of Alzheimer's disease. In most parts of the brain the local development seems to consist of subsequent stages, amyloid- β accumulation, glucose hypometabolism, cortical atrophy, and finally cognitive decline (Benzinger *et al.*, 2013). This holds for the majority of brain regions, but recent research also emphasizes that the local relationship between amyloid- β deposition and glucose hypometabolism, as well as cortical atrophy, is not consistent throughout the brain (La Joie *et al.*, 2012; Benzinger *et al.*, 2013).

Objective of the current study

Recent methodological developments of functional MRI analysis employing pattern classification provide a novel approach for investigating memory (Bonnici *et al.*, 2012), by determining the coding of information in distributed patterns rather than by comparing brain activity levels in a voxel-wise fashion. This methodology is particularly effective in the analysis of ultra high-field (7 T) functional imaging data (Bode *et al.*, 2011). As musical memory is known to be well preserved in many Alzheimer's disease case studies, we hypothesized that the late-degenerating brain structures in Alzheimer's disease (namely the motor cortices, the anterior cingulate gyrus and the orbitofrontal cortex) play a fundamental role in encoding long-known music (Frisoni *et al.*, 2007; Baird and Samson, 2009). This hypothesis corresponds to the findings of a previous study comparing verbal and musical memory retrieval, which indicated that these regions are involved in musical memory retrieval (Groussard *et al.*, 2010).

The current study examined patterns of blood oxygen level-dependent activations, acquired with ultra high field 7 T functional MRI. We used three different stages of exposure to a musical stimulus (unknown, recently known, long-known). We expected that a set of brain regions different from those crucial to encoding long-known music would be critical for mediating first time exposure effects of the music. In addition to the two conditions, long-known music and unknown music, that are obviously required to determine brain networks mediating the processing of long-known music, we introduced a third experimental condition, recently-known music, which enabled discrimination between first time exposure effects and long-known music encoding. This is based on the observation that listening to a song twice already increases implicit memory and liking for it, as well as decreases the potential for the stimulus being received as negative or potential threat, which are aspects we summarize as first time exposure effects (Hunter and Schellenberg, 2010). The functional MRI data were analysed with multivoxel pattern classification using the spherical searchlight approach of Kriegeskorte *et al.* (2006). We compared these results with probability maps of cortical atrophy, hypometabolism and amyloid- β deposition acquired from a group of 20 patients with Alzheimer's disease and 34 healthy control subjects (La Joie *et al.*, 2012).

Materials and methods

Experiment 1: Musical memory

Participants: functional MRI experiment

Thirty-two healthy right-handed participants, with unimpaired hearing abilities and normal or corrected-to-normal vision (wore glasses), took part in the study. Their age range was 24 to 32, with a mean age of 28.0 ± 2.2 years, 16 male and 16 female. All participants were of German nationality and their mother tongue was German. None of them was a professional musician; however, 17 participants had learned a musical instrument during their lifetime. Only three were still playing an instrument by the time the experiment was carried out. All participants gave informed written consent in accordance with the local ethics research committee and were paid for their participation.

Stimulus selection

Song stimuli were chosen such that each long-known song was associated with two unknown songs with similar characteristics (genre, mood, composition style, etc.). Thus, one long-known and two unknown songs formed a 'song triplet', which had similar features. The long-known songs were selected from the German 'media control charts list' of top 10 songs from 1977–2007 (<http://www.officialcharts.de/>), as well as a variety of nursery rhymes and oldies. A pre-selection of putatively similar unknown songs (later condensed by subject ratings, see below) was made using the large-scale statistical assessments of listening habits provided by websites such as

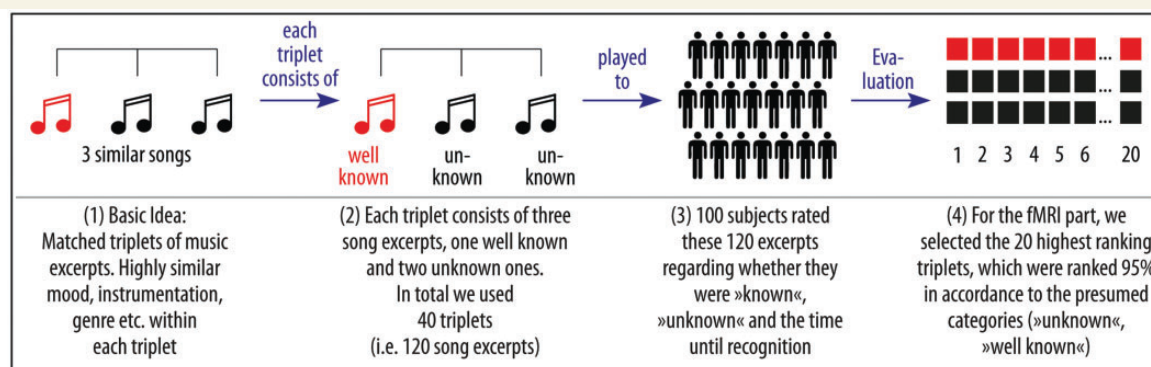


Figure 1 Stimuli validation experiment. Behavioural pilot experiment to select musical stimuli. (1) Basic idea: matched triplets of music excerpts. Highly similar mood, instrumentation, genre, etc. within each triplet. (2) Each triplet consists of three song excerpts, one well known and two unknown. In total we used 40 triplets (i.e. 120 song excerpts). (3) One hundred subjects rated these 120 excerpts regarding whether they were 'known', 'unknown' and the time until recognition. (4) For the functional MRI (fMRI) experiment, we selected the 20 highest ranked triplets, which were rated 95% in accordance to the presumed categories ('known', 'unknown').

www.last.fm, www.amazon.com, www.pandora.com, and by informed matching carried out by musical experts.

We acquired a total of 40 triplets, corresponding to 120 songs. For each song, a 20-s excerpt was selected, representing the most characteristic and recognizable segments of this song. This selection of triplets was further reduced, so that only the triplets with maximal recognition of the long-known songs and minimal recognition of the unknown songs entered the functional MRI experiment. For this, we performed a behavioural validation experiment with 100 subjects. To avoid any familiarization with the unknown songs, the subjects for this behavioural preselection experiment did not participate in the actual functional MRI experiment. The subjects were asked to rate the songs with regard to recognition, liking, and autobiographical connections. Recognition was rated on a 3-point scale (unknown, maybe familiar, definitively recognized). Liking was rated on a 5-point scale, where 1 was 'didn't like at all' and 5 was 'liked it a lot'. The time until recognition was also monitored. While subjects listened to the music, they noted the time when they recognized the song. If there was no recognition, the field was left blank. We then selected the top 20 song triplets for our functional MRI experiment, so we only included the triplets where the long-known songs were familiar while the unknown songs were novel (Fig. 1).

One hundred healthy participants, with unimpaired hearing abilities and normal or corrected-to-normal vision (wore glasses), took part in the behavioural validation experiment. The age range was 21 to 48, with a mean age of 29.6 ± 5.5 years, 47 male and 53 female. All participants were of German nationality and their mother tongue was German. All participants gave informed written consent in accordance with the local ethics research committee and were paid for their participation. Subjects of the behavioural validation experiment did not participate in the functional MRI experiment.

Experimental procedure: familiarization task

One hour prior to scanning, a familiarization task was performed. The participants were exposed twice to half of the unknown songs (i.e. one song per triplet). Each participant was presented with a unique randomized assignment of

unknown songs during the listening task (i.e. we randomly chose one of the two unknown songs of each triple for each subject). The songs were presented in a randomized order. To maintain attention during the familiarization task, the subjects replied to a randomized music-related question after each song on the computer screen (e.g. whether they heard a guitar or vocals in the song excerpt). Ultimately each participant had a unique list of recently known and unknown songs, while sharing the long-known songs (Fig. 2).

Experimental procedure: functional MRI experiment

The scanning paradigm was comprised of five experimental runs, each run consisted of 12 trials. The trials consisted of 20-s stimulus presentation and 8-s rating (whether the song was liked and whether the song was known). The order of presentation was randomized, with the constraint that for each run the number of trials of each experimental condition (long-known, recently known, and unknown) was identical (four trials of each condition per run). The duration of each run was ~ 5.6 min; the total functional scanning time was ~ 28 min (Fig. 3).

Scanning parameters

We used an ultra-high-field 7 T whole-body magnetic resonance scanner (MAGNETOM 7T, Siemens Healthcare) with a combined birdcage transmit and 24-channel phased array receive RF coil (NOVA Medical Inc). This equipment provided an exceptionally high signal-to-noise ratio at high spatial resolution. We chose to scan at an isotropic resolution of 1.9 mm; blood oxygen level-dependent contrast images were acquired with a gradient-echo EPI sequence (echo time = 20 ms, repetition time = 2000 ms, 58 slices). The image coverage included the entire brain, excluding the lower cerebellum and brainstem. Anatomical 3D images were acquired after the functional sessions using an MP2RAGE (Marques et al., 2010) sequence at an isotropic resolution of 0.9 mm (sequence identification: MP2RAGE, repetition time = 5000 ms, pat2). We used MRI compatible in-ear headphones (S14, Sensimetrics). Additionally, we used within-ear shielding to improve acoustical attenuation. We achieved this by forming a custom silicone earmuff

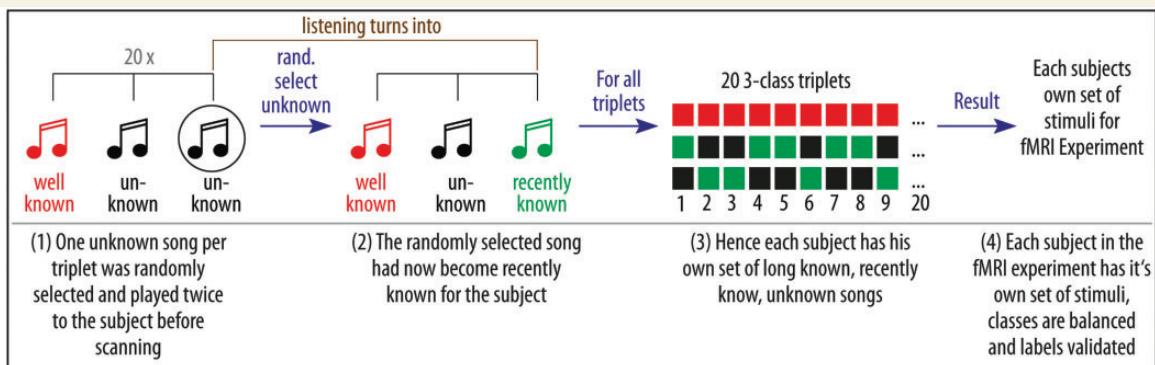


Figure 2 Constructing third experimental class. Familiarization task and constructing experimental class 'recently known'. (1) One unknown song per triplet was randomly selected and played twice to the subject before scanning. (2) The randomly selected song had now become 'recently known' for the subject. (3) Hence each subject had his own set of long-known, recently known and unknown songs. (4) Each subject in the functional MRI (fMRI) experiment had their own unique set of stimuli; classes are balanced and labels validated. rand. = random.

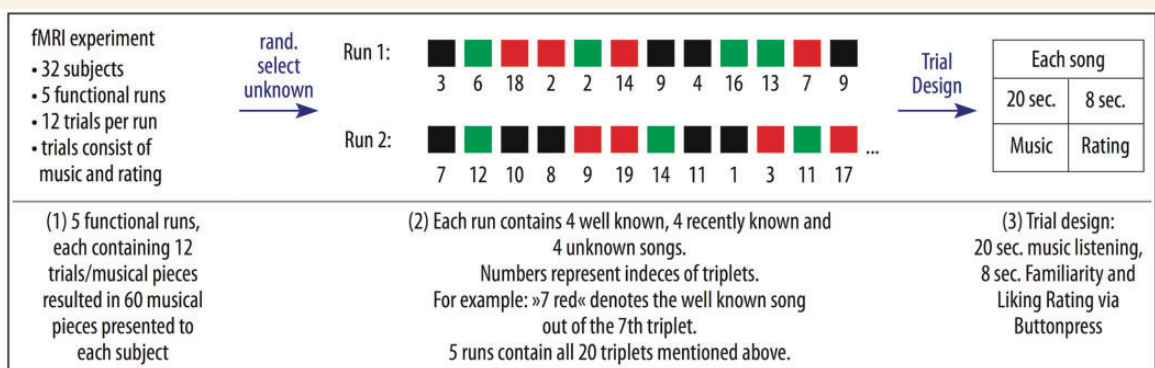


Figure 3 Functional MRI experiment design. (1) Five functional runs, each containing 12 trials/musical pieces, which resulted in 60 musical excerpts presented to each subject. (2) Each run contained four long-known, four recently known and four unknown songs. Numbers represent indices of triplets. For example: '7 red' denotes the well-known song out of the seventh triplet. Five runs contain all 20 triplets mentioned above. (3) Trial design: 20-s music listening, 8-s familiarity and liking rating via button press. fMRI = functional MRI; rand. = random.

for each subject. The attenuation of scanner noise provided by the combined headphones and silicone earmuffs allowed us to use a continuous scanning scheme, as opposed to sparse sampling. Visual presentations (fixation cross during music presentation and ratings afterwards) were projected with an LCD projector via a mirror onto a screen in the scanner. For all stimuli, 'Presentation' software by Neurobehavioral Systems with custom code was used.

Image analysis

Preprocessing of the functional MRI data was performed with SPM8 (Statistical Parametric Mapping, FIL, Wellcome Trust Centre for Neuroimaging Institute of Neurology, UCL, London), and included head motion correction and spatial normalization to the MNI305 space. High-pass filtering was applied using a cut-off frequency of 1/70 Hz. For each run and condition, we computed a map of estimated beta parameters using SPM8. The temporal onsets for beta-estimation were determined by the behavioural stimulus-selection experiment, where subjects were asked to indicate the times at which the songs were recognized. We used the average recognition time

over all songs as onsets for a boxcar condition function, which was 6 s. This function was convolved with the standard haemodynamic response function of SPM8 to form a regressor.

General linear model preprocessing resulted in five beta-maps per experimental condition for each participant, i.e. a total of 15 beta-maps per subject. The beta-estimates were used for a whole-brain searchlight decoding procedure. The searchlight diameter was set to seven voxels, corresponding to a radius of 13.3 mm. For classification, we used a linear support-vector-machine classifier (Chang and Lin, 2011). The support-vector-machine type was C-SVC, with a linear kernel, and all other parameters were set to default. The resulting accuracy maps were corrected for multiple comparisons using a non-parametric framework, based on permutation tests on single subject level combined with a Monte-Carlo resampling procedure on the group level (Stelzer *et al.*, 2013). On the single subject level we employed 100 permutations, which were recombined into 10^5 chance maps on the group level. The voxel-wise threshold was set to $p_{\text{vox}} = 0.001$; the cluster threshold was set to $p_{\text{cl}} = 0.05$.

Experiment 2: Comparing musical memory and Alzheimer's disease anatomy

Voxel-wise maps of atrophy, hypometabolism and amyloid- β deposition were derived from a separate experiment including 20 patients with Alzheimer's disease and 34 normal control subjects included in the IMAP project (Caen, France). None of the subjects had ever been professional musicians. Patient selection, data acquisition and image processing have been described in detail in previous work (La Joie *et al.*, 2012), thus we only provide a brief summary below.

The patients included in the present study fulfilled clinical criteria for probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann *et al.*, 1984). In addition, they were shown to have positive biomarkers for both amyloid- β deposition and neurodegeneration (La Joie *et al.*, 2012), indicating a high probability of Alzheimer's disease aetiology according to recent recommendations from the National Institute on Aging and Alzheimer's Association (NIA-AA) workgroup (McKhann *et al.*, 2011). Control subjects (i) had no history of clinical evidence of major neurological or psychiatric disorder; (ii) performed in the normal range on a battery of cognitive tests; and (iii) had no evidence of amyloid- β deposition (La Joie *et al.*, 2012).

The probable Alzheimer's disease patient group consisted of 20 subjects, 10 male and 10 female, with a mean age of 68.9 ± 9.0 years and a Mini-Mental State Examination (MMSE) score of 20.6 ± 4.5 . The healthy control group consisted of 34 subjects, 14 male and 20 female, with a mean age of 68.1 ± 7.2 years and a MMSE of 29.1 ± 0.8 . All participants underwent structural T_1 -weighted MRI on a 3 T scanner and PET using both FDG to assess glucose metabolism and ^{18}F -florbetapir to quantify amyloid- β deposition. MRI data were segmented, normalized, and modulated using the VBM5.1 toolbox, implemented in the Statistical Parametric Mapping 5 (SPM; Statistical Parametric Mapping, FIL, Wellcome Trust Centre for Neuroimaging Institute of Neurology, UCL, London) software to obtain maps of local grey matter volume corrected for brain size. Both FDG and florbetapir PET data were corrected for partial volume effects, normalized using the deformation parameters defined from the MRI procedure and quantitative scaled using the cerebellar grey matter as a reference to obtain standardized uptake value ratio images.

For each imaging modality, the effect of age was modelled in each voxel from the healthy control group, enabling us to compute a specific age-adjusted predicted map for each patient. Each patient's image was then compared to his/her specific age-adjusted map to obtain voxel-wise W -score (age-adjusted Z -score) maps. Finally, W -score maps were averaged across the 20 patients for each of the three modalities. Average W -score maps were reversed so that positive W -values indicate pathological features in all three modalities (less grey matter, less glucose metabolism, more amyloid- β deposits). This resulted in three group-level maps of atrophy, hypometabolism and amyloid- β , all being expressed in the same unit (see La Joie *et al.*, 2012 for further details).

Results

The results are split into two sections. First, we report results of the musical memory experiment on 32 normal young human subjects. Second, we report W -score biomarker probability maps from 20 patients with Alzheimer's disease as compared to 34 normal human subjects. Note that there is no overlap between subjects in Experiments 1 and 2. Lastly we apply the region of interest obtained from Experiment 1 to estimate the severity of biomarker abnormalities from Experiment 2 within the musical memory region of interest as compared to the rest of the brain.

Experiment 1: Musical memory

The local multivariate information content of musical memory in a normal subject group was obtained using the searchlight decoding approach (Figs 4 and 5 and Table 1). The decoding-accuracy group maps delineated brain regions containing stimulus-related information, enabling the classifier to distinguish between paired experimental conditions (i.e. testing two classes against each other). We compared the experimental conditions 'long-known music', 'recently known music' and 'unknown music' pair-wise against each other.

We investigated long-known musical pieces versus recently known musical pieces, to gain insight into regions involved in long-term musical memory processing, and to exclude processes involved in first time musical exposure. Then we investigated long-known musical pieces versus unknown musical pieces, to explore overlaps with the previous comparisons. Finally we compared recently known musical pieces with unknown musical pieces for validation purposes. The group decoding-accuracy maps showed very stable results, with accuracies up to more than 20% over chance level in the significant regions (i.e. accuracies > 0.7 , where the chance level is 0.5).

To clarify the relation between our findings and Alzheimer's disease progression, in Experiment 2 we analysed the spatial patterns of three Alzheimer's disease biomarkers, namely cortical atrophy, hypometabolism and amyloid- β deposition, which are well-studied hallmarks of Alzheimer's disease. We then compared the biomarker values within the musical memory region of interest obtained from Experiment 1 to the rest of the brain and found that the region of interest identified to encode musical memory is indeed relatively spared in Alzheimer's disease.

Multivariate pattern analysis group

Long-known versus recently known

The results in Fig. 4 show the decodability of the two different brain states elicited by listening to long-known and recently known music, using multivariate decoding with a searchlight of 13.3 mm diameter. The functional data are overlaid on an average structural image combining the

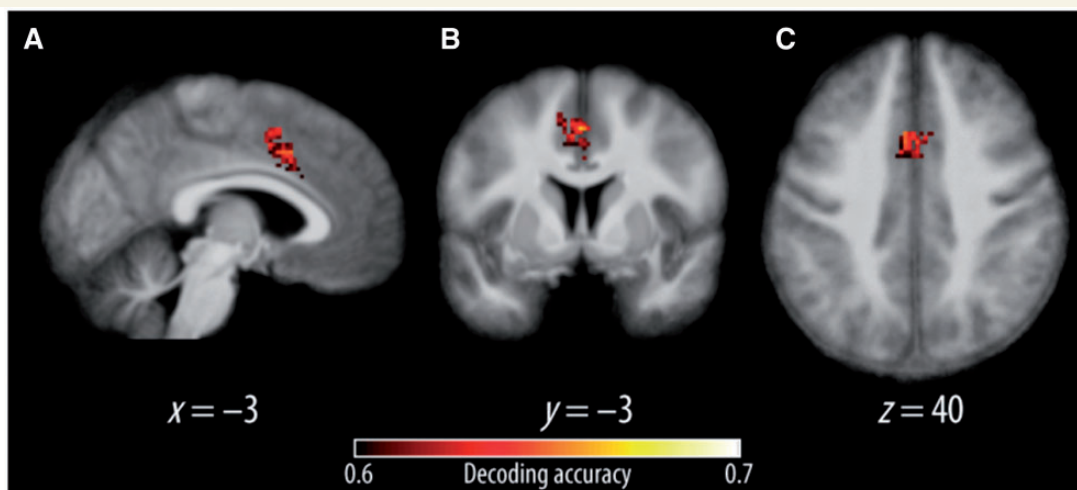


Figure 4 Multivariate pattern analysis results: long-known versus recently known music. We show cluster size corrected accuracy maps (permutation statistics, corrected for multiple comparison, voxel-wise threshold $P = 0.001$). x , y and z denote the MNI coordinates of the selected sagittal (**A**), coronal (**B**) and axial (**C**) slice. The colour bar indicates the significance of the decoding accuracies (e.g. 0.6 indicates 10% over chance and 0.7 indicates 20% over chance).

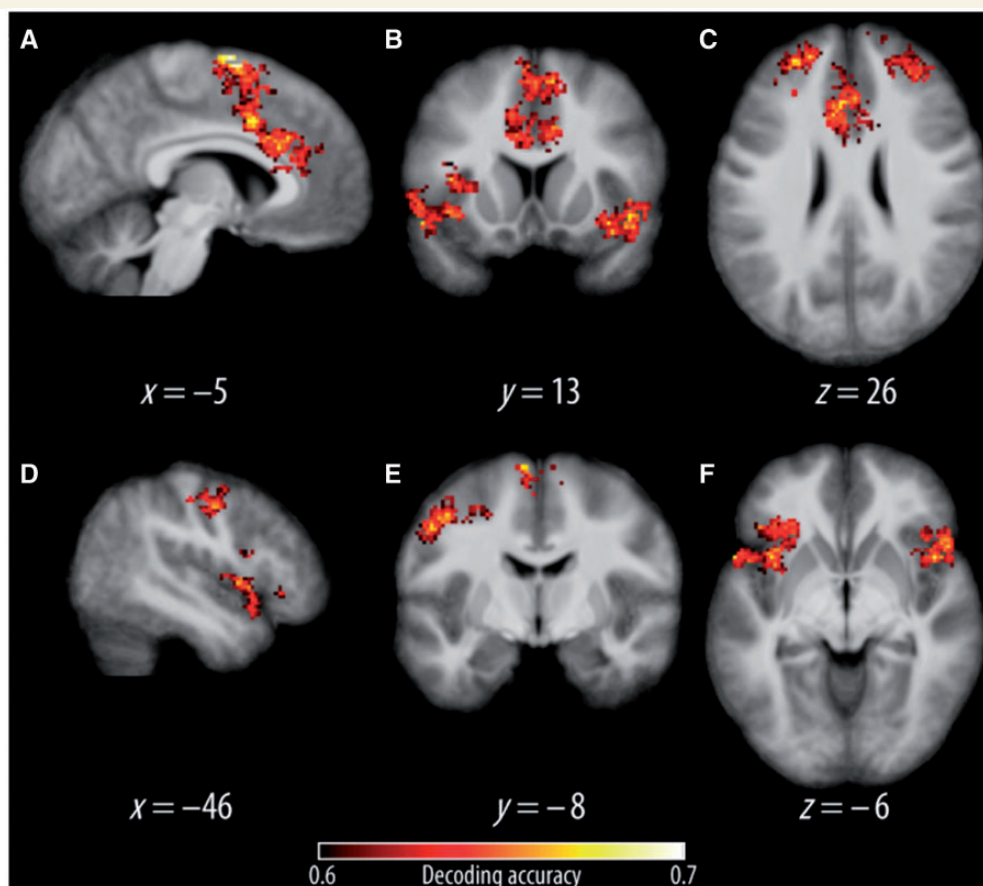


Figure 5 Multivariate pattern analysis results: long-known versus unknown music. Shown are cluster size corrected accuracy maps (permutation statistics, corrected for multiple comparison, voxel-wise threshold $P = 0.001$). x , y and z denote the MNI coordinates of the selected sagittal (**A** and **D**), coronal (**B** and **E**) and axial (**C** and **F**) slices. The colour bar indicates the significance of the decoding accuracies according to Table 1.

Table 1 Functional MRI results

Anatomical region	Cluster size	Accuracy	MNI coordinates (x, y, z)
Long-known versus recently known			
Caudal anterior cingulate gyrus and ventral pre-SMA	423	0.66	−1, 4, 46
Long-known versus unknown			
Anterior cingulate gyrus and pre-SMA	2466	0.70	3, 9, 56
Frontal pole (L)	634	0.68	−26, 48, 23
Frontal pole (R)	552	0.68	36, 41, 23
Temporal pole and insular cortex (L)	1247	0.67	−29, 17, 5
Temporal pole and insular cortex (R)	555	0.68	40, 17, −16
Precentral gyrus (L)	541	0.67	51, −9, 41

Results of Figs 4 and 5. Cluster sizes are reported over a combination of different regions, if a cluster was spreading across more than one anatomical structure. Corrected accuracies are reported at the maximum within the corresponding cluster. MNI-coordinates are also reported at the corresponding accuracy maxima of each cluster.

MP2RAGE scans of all 32 subjects. We found statistically significant decoding accuracies (corrected for multiple comparisons) in the caudal anterior cingulate gyrus. Furthermore we were able to decode the two conditions in the ventral pre-supplementary motor area (pre-SMA).

Long-known versus unknown

The results in Fig. 5 show the searchlight decodability of the different brain states for passive listening to long-known and unknown songs, using the same searchlight diameter as before. The results were corrected for multiple comparisons as before. Significant decoding accuracies were found in the caudal anterior cingulate gyrus and ventral pre-SMA. Both regions exhibited stimulus-based information that discriminated between long-known and recently known music. By contrast with the comparison above (long-known versus recently known), the results show several more brain areas. We observed informative regions discriminating long-known and unknown music in bilateral frontal pole, temporal pole, and insular cortex. Additionally, the left precentral gyrus/motor cortex showed differential encoding of the two brain states.

Recently known versus unknown

Whole-brain searchlight decoding between recently known against unknown music yielded no significant results when including the multiple comparisons correction. However, when the analysis was constrained to the regions of interest, already shown to be involved in long-known music encoding (Figs 4 and 5), decoding accuracies were significantly above chance. The first of these regions of interest was derived from the thresholded accuracy map of long-known versus unknown music and the second region of interest consisted of the thresholded accuracy map from long-known versus recently known music. The sizes of the regions of interest were 423 voxels and 5995 voxels, respectively. The cross-validation scheme and non-parametric statistics were identical, with the omission of whole-brain testing for multiple comparisons. Constraining classification to these regions of interest made it possible to decode recently known music against unknown music. The mean accuracy for the long-known versus unknown mask was 0.58, with a *P*-value of 0.0084.

The region of interest from the recently known music versus unknown music comparison yielded a mean decoding accuracy of 0.574, with a *P*-value of 0.0131.

Experiment 2: Musical memory and Alzheimer's disease

Biomarker region of interest comparison

Figure 6 displays a rendered view of the identified musical memory region of interest and *W*-score maps of cortical atrophy, hypometabolism and amyloid- β deposition derived from 20 patients with Alzheimer's disease and 34 normal control subjects. Furthermore we parcelled each biomarker *W*-score map with a grey matter masked resting state parcellation atlas (Craddock et al., 2012) to achieve similar smoothing and comparability between all anatomical locations and the musical memory region of interest. Thus each parcel was constrained to have a similar number of voxels to the musical memory region of interest, which contained 2773 voxels after it was co-registered with the *W*-score biomarker maps and the parcellation atlas. We chose the parcellation with mean parcel size of 3126 ± 1073 voxels to achieve comparability between regions, which was accordingly a parcellation of the maps into 450 grey matter parcels. The mean biomarker values for each parcel are displayed in the histograms, and the mean biomarker value within the musical memory region of interest is indicated in each histogram with a coloured line (Fig. 6 B). The parcellation-based analysis on voxel-based morphometry *W*-score maps revealed that mean grey matter loss *W*-score within the musical memory region of interest was lower than in 98% of all parcels. The atrophy *W*-score within the musical memory region of interest was 0.012, whereas the mean *W*-score of all grey matter parcels was 0.508. With respect to grey matter atrophy, the musical memory region of interest was located in regions that are significantly less affected compared to the rest of the brain; the greatest atrophy can be found in temporal, inferior parietal cortex, and precuneus. All of these regions are strongly associated with memory functions (Cabeza et al., 2008).

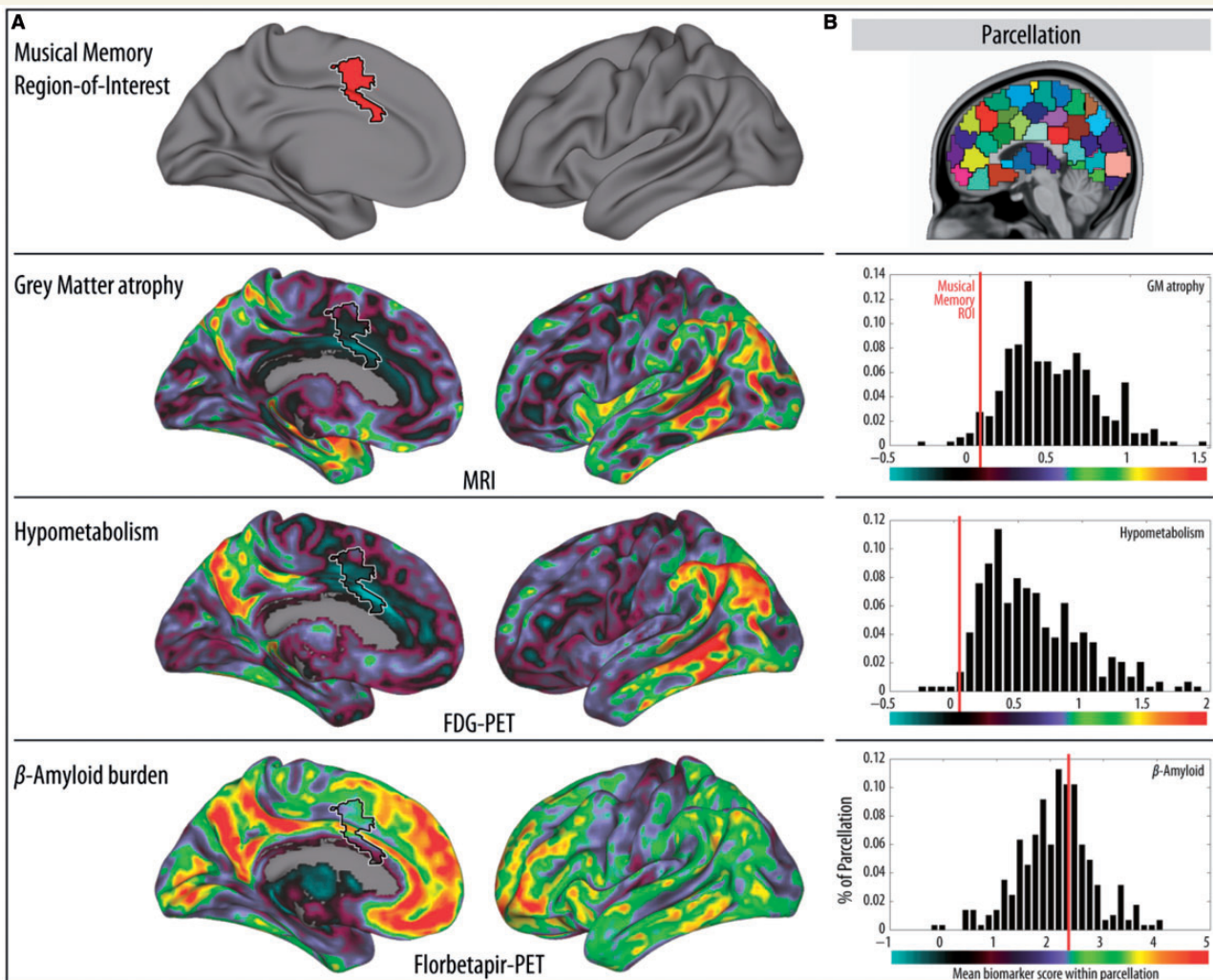


Figure 6 Musical memory region of interest and Alzheimer's disease biomarkers. **(A)** Qualitative comparison between Alzheimer's disease biomarker maps and the musical memory region. The *top* row shows the musical memory region of interest (red) on a 3D brain render. The musical memory region of interest is shown as a white coloured contour in rows two to four, overlaid on the W-score biomarker maps. For the sake of clarity, and because all W-score maps and the musical memory region of interest were highly symmetrical, only the left hemisphere is displayed. The *second* row shows rendered surfaces and overlaid W-score maps of cortical atrophy. The *third* row displays the hypometabolism W-score map analogous to the second row. The *bottom* row shows amyloid- β deposition as W-score maps accordingly. Colour scales were adapted to each biomarker map and are presented under each corresponding histogram. **(B)** For a quantitative comparison, we computed the mean biomarker values inside of the musical memory region of interest and the mean biomarker value within other regions of interest of similar size accordingly (see 'Materials and methods' section). A view of the parcellation mask is shown in the *top* row on the right side. In the three histograms below, each black bar represents the frequency of parcels (*y*-axis) with a certain mean biomarker value (*x*-axis). The red line depicts the mean biomarker value within the musical memory region of interest. Each histogram shows the corresponding biomarker (e.g. the top one depicts the grey matter atrophy). GM = grey matter.

Similar to grey matter atrophy, the spatial distribution of hypometabolism is found mostly in the precuneus, in the posterior cingulate gyrus, and in temporal as well as parietal cortices. Again the musical memory region of interest was located within a region that was significantly lower for this biomarker, such that 97% of the parcels had a higher hypometabolism W-score. Within the musical memory region of interest, we found a mean W-score of 0.067, whereas the mean W-score of all other parcels was 0.618.

For the amyloid- β burden biomarker, however, the musical memory region of interest was not in a region with significantly lower values. Indeed, the mean W-score in this region was even higher than the mean of all parcels, so that only 37% of all parcels showed a higher mean amyloid- β W-score than the musical memory region of interest. Within the musical memory region of interest, the mean amyloid- β deposition W-score was 2.330, whereas the mean of all other parcels was 2.103. Amyloid- β deposition

was predominantly found in the medial and orbital prefrontal cortex, precuneus and posterior cingulate. The primary sensorimotor cortex, occipital cortex, thalamus, and medial temporal lobe were relatively spared.

Discussion

In this study we compared the brain areas that encode long-known music with the anatomy of Alzheimer's disease degeneration. The results offer a potential explanation of why musical memory is so surprisingly well preserved in many patients with Alzheimer's disease. Figure 6 shows both the brain regions involved in long-term musical memory coding (as detected by classifying long-known against recently known musical pieces), and the different biomarker W-score maps showing differences between patients with Alzheimer's disease and normal control subjects. Interestingly, the pattern of cortical degeneration and hypometabolism in Alzheimer's disease shows practically no overlap with the network that we have observed as crucial for long term musical memory encoding. In fact, the musical memory region features among the lowest grey matter atrophy and hypometabolism values of the entire brain. Previous literature further confirms that ventral pre-SMA and caudal anterior cingulate gyrus are among the regions last to degenerate during Alzheimer's disease and also show little to no significant cortical atrophy as well as hypometabolism (Frisoni *et al.*, 2007, 2010; La Joie *et al.*, 2012; Benzinger *et al.*, 2013; Jack and Holtzman, 2013; Gordon *et al.*, 2014). Amyloid- β deposition was not significantly lower in the musical memory region of interest than in the rest of the brain. This is consistent with the idea that this region is still in a very early stage of biomarker development. While the sequence of biomarkers may change according to brain regions (La Joie *et al.*, 2012; Chételat, 2013), amyloid- β deposition is expected to precede cortical hypometabolism and atrophy in this brain area. Although there is substantial amyloid- β deposition within the region of interest, no significant cortical atrophy or hypometabolism is typically observed in this region (Gordon *et al.*, 2014). Instead, it seems to be relatively well preserved, and recent research also observed an enhanced connectivity between the anterior cingulate gyrus and other nodes of the salience network during Alzheimer's disease, leading to the suggestion that it may compensate decreased brain functionality in Alzheimer's disease (Zhou *et al.*, 2010; Brier *et al.*, 2012; Benzinger *et al.*, 2013).

Using multivariate pattern classification and ultra-high field scanning at 7 T, we have observed both the ventral pre-SMA and the caudal anterior cingulate gyrus to be crucial for the encoding of long-term musical memory. The current data thus offer a potential neuroanatomical explanation for the preservation of long-term musical memory in Alzheimer's disease. The prominent role of ventral pre-SMA and caudal anterior cingulate gyrus is further consistent with the lesion case studies reviewed above,

where case studies showing intact musical memory and impairment of other types of memory never report damage to pre-SMA and caudal anterior cingulate gyrus.

Although the brain regions we observed to be involved in long-term memory of music (pre-SMA and anterior cingulate gyrus) have been associated with procedural and short-term memory functions, as well as being predictive of subsequent memory encoding in younger and older adults (Lee and Quessy, 2003; Morcom *et al.*, 2003; Jackson *et al.*, 2006; Aharoni *et al.*, 2013), they are not usually considered to be crucial to musical memory. However, recent functional MRI studies have shown the same regions to be involved when neural correlates of music familiarity were analysed. These previous studies were aimed at investigating different aspects associated with music familiarity, and thus correspondingly revealed different brain regions than the musical memory region identified in the current study. Demorest and colleagues (2009) investigated music familiarity and cultural context and observed that culturally familiar musical stimuli were more easily acquired than culturally unfamiliar ones. Contrasting the more familiar with the less familiar musical pieces revealed significant activations in the same region that we observed for long-known versus recently-known musical pieces. Pereira and colleagues (2011) investigated the effect of music familiarity on music-related emotions and showed that the caudal anterior cingulate gyrus and ventral pre-SMA are involved in long-known versus recently-known song stimuli presentation. Another recent study, investigating music-evoked autobiographical memory also found our observed region of interest to be related to the familiarity of musical pieces (Janata, 2009). The author also noted that activity in this region is not correlated with the autobiographical saliency of the familiar musical pieces. This suggests that the cortical area we have discovered is not particularly sensitive to the autobiographical relevance of the musical pieces heard. In addition, Groussard and colleagues (2010) discovered the caudal anterior cingulate gyrus, the ventral pre-SMA in an automatic semantic musical memory retrieval task, related to the degree of music familiarity.

This body of research strongly supports the pre-eminent role that we have observed in long-term musical memory for the caudal anterior cingulate gyrus and the ventral pre-SMA. The decoding of long-known music versus unknown music involves brain areas additional to those involved with long-known versus recently known music (Figs 4 and 5). Accordingly, it seems plausible that the observed differences between the two analyses in the temporal poles, bilateral insular cortices, rostral anterior cingulate and the frontal pole are largely due to first time exposure effects, which may not play a role in long term neural representation. This notion is further supported by the fact that classification of recently known versus unknown music slightly improves when including brain areas that are essential to classification of long-known versus unknown (as opposed to long-known versus recently known) music.

Research into the anatomy of musical memory commonly suggests that the temporal lobes have an important musical memory function (see 'Introduction'). However, two findings argue for a perhaps redundant role of the temporal lobes in long-term musical memory. Alzheimer's disease affects temporal lobes very early, as shown in Fig. 6, but long-term musical memory is largely spared. Furthermore, patients with severe temporal lobe damage and also temporal pole damage show relatively intact long-term musical memory (Ayotte *et al.*, 2000; Samson and Peretz, 2005; Tsapkini *et al.*, 2011; Finke *et al.*, 2012). Conversely, a case study observed severe bilateral temporal lobe lesions that were accompanied by severely impaired musical memory abilities, while other memory systems remained largely preserved (Peretz, 1996). However, the author also reports preserved indirect musical memory abilities in cued memory tasks. These findings suggest that while the temporal lobes may be involved in explicit musical memory, their role in long-term musical memory processing may not be essential to maintain long-term representations of music. Furthermore the temporal lobe, and especially temporal pole areas, may be necessary to encode new musical memory, and once musical memories are encoded these areas might not be needed for memory retrieval (Olson *et al.*, 2007; Jonides *et al.*, 2008; Hsieh *et al.*, 2011). This supports the suggestion of Baird and Samson (2009) that mostly implicit musical memory might be spared in Alzheimer's disease and thus our study gives a possible explanation for the preservation of long-term musical memory after severe bilateral temporal lobe damage (as in Alzheimer's disease), since we show that long-term musical memory representations heavily rely on ventral pre-SMA and the caudal anterior cingulate gyrus.

The ventral pre-SMA and caudal anterior cingulate have been associated with a variety of different cognitive functions. There is evidence suggesting that both regions cooperate in sequence planning and evaluation (Nachev *et al.*, 2008), though the exact function is not yet completely clear. The pre-SMA has been shown to be concerned with complex sequence planning, task switching, resolving conflicts and sequence learning; for instance, increased activity in this region was observed when musical sequences played on a keyboard were disrupted by delay or false notes (Pfordresher *et al.*, 2014).

The caudal anterior cingulate gyrus has been suggested to be crucial in decision-making and also in learning. Some of its main function seems to be prediction, expectation and subsequent evaluation of future events (Shenhav *et al.*, 2013). There is thus evidence that the observed region of interest has a role in complex planning and constant evaluation (Rushworth *et al.*, 2007), which is likely to be crucial to musical memory, as music is a rhythmic, multimodal sequence of structured sounds (Koelsch, 2014). This proposed function for pre-SMA and caudal anterior cingulate gyrus also further corroborates that in Alzheimer's disease implicit, rather than explicit musical memory is spared. Our findings may give a possible explanation of the

observed split between sparing of these two kinds of musical memories (Baird and Samson, 2009), and may thus provide a basis for future research on the most basic neural correlates of music representation.

To our knowledge the current study is the first that uses objective data and cutting-edge methodology to demonstrate that the regions normally involved in musical memory encoding are strikingly well preserved in Alzheimer's disease. This may well underlie the observed preservation of musical memory in Alzheimer's disease although this evidence is so far indirect. It would be highly desirable, though perhaps difficult in practice, to test the hypothesis further in a study with actual Alzheimer's diseased patients, testing for musical memory, and potentially collecting functional MRI data of musical memory.

In conclusion, our results suggest a neuroanatomical explanation for the preservation of musical memory in many Alzheimer's disease cases, and provide evidence for an encoding of musical memory in brain regions that are affected only at late stages of Alzheimer's disease.

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