Neural Basis of Long-term Musical Memory in Cognitively Impaired Older Persons

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Objective: The objective of this study was to determine whether exposure to long-known music would evoke more extensive activation of brain regions minimally affected by Alzheimer disease (AD) pathology and outside traditional memory networks using a functional magnetic resonance imaging paradigm involving listening to long-known and recently-learned music in older adults with cognitive impairment to provide insight into mechanisms of long-term musical memory preservation in cognitively impaired older persons.

Methods: Seventeen subjects with a diagnosis of mild AD or mild cognitive impairment were recruited for this study. Subjects were scanned using functional magnetic resonance imaging while they performed a music listening task, which included short clips of personally selected music from the patient's past and newly-composed music heard for the first time 60 minutes before scanning. From this task, we obtained group-level maps comparing brain areas associated with long-known and recently-heard music in all subjects.

Results: Exposure to long-known music preferentially activated brain regions including the medial prefrontal cortex, precuneus, anterior insula, basal ganglia, hippocampus, amygdala, and cerebellum relative to recently-heard music. These areas are involved in autobiographical memory and associated emotional responses. In addition, they are minimally affected by early stage AD pathology, thus providing a neural basis for long-known musical memory survival.

Conclusions: Long-known music activates a bilateral network of prefrontal, emotional, motor, auditory, and subcortical regions (cerebellum, putamen, limbic structures). This extensive activation, relative to recently-heard music, may offer structural and functional clues as to why long-term musical memory appears to be relatively preserved among cognitively impaired older persons.

Key Words: cognitive aging, fMRI, memory, plasticity, all neurology

(*Alzheimer Dis Assoc Disord* 2020;00:000–000)

Despite extensive efforts to identify an effective pharmacological treatment for Alzheimer disease (AD), no such interventions have yet been identified.[1] On the basis of prior research, exposure to music has been demonstrated to have a beneficial effect on memory in cognitively impaired older persons.[2] Thus, it is possible that familiar music can be leveraged as a treatment for AD.

One potential reason for sparing of musical memory in AD may be that exposure to familiar music activates brain regions minimally affected by AD pathology, such as the motor cortices, the anterior cingulate gyrus, and the orbitalfrontal cortices according to some authors.[3,4] A study by Jacobsen et al[5] supports this hypothesis, showing that brain regions related to long-known music in young adults, including caudal anterior cingulate and ventral presupplementary motor area (SMA), had minimal atrophy and disruption of glucose metabolism in AD patients. The cognitive functions subserved by these areas include complex planning and evaluation, suggesting that these brain regions may be fundamental to musical memory.[5] While interesting, the conclusions of this study are extrapolated from healthy subjects and thus do not provide an explanation as to why musical memory may be spared in AD.

In addition, there have been a few studies that have explored the effect of preferred music exposure on brain function and connectivity in patients with AD. In one study, 17 subjects with AD were given a personalized music program to listen to. Posttraining imaging showed activation of the SMA and widespread improvements in corticocortical and corticocerebellar networks, thus suggesting exposure to personalized music may improve brain function.[6] In a second study 34 patients with early onset AD were compared with healthy controls using an functional magnetic resonance imaging (fMRI) paradigm consisting of exposure to familiar/unfamiliar music (to gage semantic memory) and single/multiple exposures (to gage episodic memory). Semantic impairment localized to the right inferior cortex while episodic memory deficits localized to the precuneus and posterior cingulate gyrus.[7] Though both studies are of interest neither differentiated brain activation patterns associated with long-known versus recently-heard music in an AD cohort.

In our study, we compared brain activation patterns in older patients with cognitive impairment exposed to long-known music relative to newly-learned music. We hypothesized that exposure to long-known music would result in more extensive activation of brain regions, specifically corresponding to areas involved in emotional response and brain regions minimally affected by AD pathology.

METHODS

Experimental procedures were approved for human research by the Research Ethics Board at St. Michael's Hospital

Received for publication October 21, 2019; accepted March 18, 2020.
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Supported by Canadian Consortium for Neurodegeneration in Aging, MRRC St. Michael's Pilot Grant, Heather and Eric Donnelley Endowment (St. Michael's Hospital), and VPR/Provost Office to M.H.T.
The authors declare no conflicts of interest.
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in Toronto, ON, Canada. Informed consent was obtained by all participants. Seventeen persons diagnosed with mild cognitive impairment (MCI) or probable AD with no history of neurological or psychiatric disorder, as well as an available study partner and intact hearing, provided written consent and participated in the experiment. Individuals were assessed for disease diagnosis by a geriatric psychiatrist and/or a behavioral neurologist at the St. Michael's Hospital Memory Disorders Clinic as per the National Institute on Aging and Alzheimer's Association (NIA-AA) diagnostic criteria.[8] Assessment and diagnosis included a comprehensive patient interview, including review of the patient's subjective concerns, a thorough medical history and previous diagnoses, and objective cognitive testing.

Experimental Procedures

Preexperiment Phone Interview

Before the in-person experimental session, participants underwent a preexperiment phone interview in which musical preferences and musical experiences from the past were collected so that study personnel could create a playlist of long-known music. For the purpose of this study, long-known music was defined as recognized by the subject as his/her preferred or favorite music that held special meaning and was known to them for at least 20 years. This approach has been validated in previous studies.[9,10] During the initial phone call, the participant was asked to compile a list of at least 20 pieces of music that had been meaningful to them in some way and were asked to write down the title and artist. After the initial phone call, a second telephone interview was scheduled to give the participant time to compose the music list. During the follow-up interview, the list of music was recorded by study personnel. The music pieces were then used to compile an individualized playlist for each participant and were validated as still recognized by the participant during the experimental session of the music listening interview.

The music was purchased and collected off the iTunes music store. Recorded versions of music were selected over live versions All music selected by the participants were tonal, based on standard harmonic materials found in rock/pop, folk, and classic western music traditions with regular predominant to dominant induced cadences and tonic resolutions. The pieces contained both major and minor keys, often alternating in the same piece through modulations.

From the participants' playlist, the music coordinator randomly selected 6 songs and created 20-second music clips which were either all vocal music or all instrumental music, dependent on which type of music there existed more of on the playlist. These long-known clips were then matched in style, genre, and instrumentation to newly-composed music clips, specially composed for this study. Fifteen of 17 subjects had listened to long-known and newly-composed vocal clips and 2 participants listened to long-known and newly-composed instrumental clips.

Music Listening Interview Before Scanning

The purpose of the music listening interview before scanning was (1) to verify that the music chosen by the study personnel was, in fact, long known and still recognized to the participant, and (2) for the participants to hear newly-composed music for the first time, thereby ensuring the pieces were "recently heard" when played again during a subsequent scanning session. The participant was played music clips that were previously determined by the study personnel to be long known or recently heard by the participant. The clips were played in random order to the participant. The participant was prompted to identify the music as long known or recently heard.

Clinical Outcome Measures

A demographics questionnaire was administered with information summarized in Table 1. The Montreal Cognitive Assessment (MoCA)[11] was administered to all participants as the primary clinical outcome measure. The MoCA screening tool was designed to be sensitive enough to identify mild cognitive complaints.[11] This assessment measures 8 cognitive domains, including visuospatial and executive function (alternating trail-making, visuoconstructional skills including rectangle/cube drawing, and clock drawing), naming (naming pictures of animals), attention (forward and backward digit span, vigilance, and serial 7 s), language (sentence repetition, verbal fluency), abstraction (similarities), memory delayed recall (recalling previously encoded words), and orientation (date and location). The MoCA was more recently established to have high validity, specificity, and sensitivity.[12]

Task Design

Before scanning, all participants were given a brief training session. In the magnetic resonance imaging (MRI), participants underwent a structural scan and task-based fMRI. During the task, the participants listened to the 20-second 12 long-known and 12 recently-heard music clips. Music clips were played to the

TABLE 1. Demographic Characteristics, Baseline Cognitive Presentation of Persons With MCI, Early AD, and All Participants

	MCI (N = 13)	Early AD (N = 4)	All Participants (N = 17)
Age (y)	70.9 ± 10.1 (56-88)	79.2 ± 8.8 (70-89)	72.9 ± 10.2 (56-89)
Sex [n (%)]			
Female	11 (85)	3 (75)	14 (82)
Male	2 (15)	1 (25)	3 (18)
Education (y)	15.7 ± 2.2 (12-18)	14.5 ± 3.7 (12-20)	15.4 ± 2.5 (12-20)
Bilingual [n (%)]	5 (38)	1 (25)	6 (35)
Depression [n (%)]			
Uncontrolled	0 (0)	0 (0)	0 (0)
Controlled	3 (23)	0 (0)	3 (18)
None	10 (77)	4 (100)	14 (82)
MMSE total score	27.3 ± 1.3 (25-29)	26 ± 2.2 (23-28)	27.0 ± 1.6 (23-29)
MoCA total score	23.1 ± 2.0 (19-25)	22.2 ± 2.6 (20-26)	23.1 ± 2.1 (19-26)

The table shows the demographic information for persons with MCI or early AD diagnosis, as well as all patients.
Results are reported in mean ± SD (minimum-maximum) unless stated otherwise.
AD indicates Alzheimer disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

participant alternating between long-known and recently-heard clips, with 16 seconds of Gaussian white noise in between. The fMRI protocol was created on E-Prime software (version 2.0). Before the scan begun, the participants were given instructions to engage in the music listening, to think about whether the music was known to them, and to try to recall when/if they had heard the music from their remote past. In addition, they were told to keep their eyes closed, and try not to move their head or other parts of their body (such as finger tapping, toe tapping, humming, or mouthing the words), which can result in head movement and additional motor activation.

MRI Acquisition

The MRI scanning was conducted on research-dedicated 3.0-T Siemens Magnetom Syngo Skyra scanner with a standard multichannel head coil. An anatomic scan was acquired with T1-weighted imaging magnetization prepared rapid gradient-echo [MPRAGE; echo time (TE) = 2.54 ms, repetition time (TR) = 2000 ms, 176 slices, thickness = 1.0 mm, gap = 0 mm, field of view (FOV) = 256 mm, 1.0 × 1.0 × 1.0 voxels]. Blood-oxygenation-level dependent fMRI was acquired during the music listening task, using T2*-weighted fast echoplanar images [echo time (TE) = 30.0 ms, TR = 2000 ms, 32 slices, thickness = 4.0 mm, gap = 0.5 mm, field of view (FOV) = 200 mm, 3.1 × 3.1 × 4.0 voxels].

Preprocessing of fMRI Data

Processing and analysis of individual subject data was performed using the Analysis of Functional Neuroimages (AFNI) package (https://afni.nimh.nih.gov) and customized software developed in the laboratory. After discarding the first 2 and last 2 scan volumes of each run, rigid-body motion correction was performed (AFNI 3dvolreg), followed by the replacement of outlier scan volumes with values interpolated from neighboring scans (SPIKECOR; https://nitric.org/projects/spikecor), slice timing correction (AFNI 3dTshift), spatial smoothing by convolving images with a 6-mm full width at half maximum isotropic 3D Gaussian kernel (AFNI 3dmerge), along with regression of motion parameters (based on the first 2 principal components of the 6 rigid-body motion parameters), and linear trends as nuisance covariates. A data-driven physiological noise correction algorithm (PHYCAA+; https://nitric.org/projects/phycaa_plus) was used to spatially down-weight brain voxels with non-neural signal, follow by the regression of white matter signal, based on a seed taken from the MNI125 atlas.

To perform group-level analyses, the fMRI data were also spatially aligned to the MNI152 anatomic template using the FMRIB Software Library (FSL) software package (https://fsl.fmrib.ox.ac.uk). The FSL flirt algorithm was used to obtain the rigid-body transform of each subject's mean fMRI volume to their T1-weighted anatomic image, followed by the 12-parameter affine transform of the T1-weighted image to the template. The affine transformation matrices were then combined and applied to the fMRI data.

Analysis

Analysis of fMRI Data

For each participant, the processed fMRI data were analyzed by obtaining the task design matrix for each of the 3 conditions (fixation, recently heard, long known), convolved with the SPMG1 canonical hemodynamic response function (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dDeconvolve.html) followed by regression onto the blood-oxygenation-level dependent response for each brain voxel using a general linear model, to obtain beta coefficients for each condition. Task contrasts of interest were then obtained as the difference in regression coefficients (long known—fixation; recently heard—fixation; long known—recently heard), and a z-scored reproducible brain map was then obtained for each subject and task contrast of interest, using the split-half statistical procedure outlined in Strother et al.[13]

For each task contrast, a group-level 1-sample t test was conducted on the set of individual z-scored brain maps at each voxel, to identify brain areas associated with long-known and recently-heard music in all subjects. For all group-level t-statistic maps, thresholding was performed at a voxel-wise level of $P = 0.005$, followed by cluster-size thresholding at a minimum size of 20 contiguous voxels to adjust for multiple comparisons. We conducted subanalyses of brain activation results comparing participants with AD and MCI to determine whether the overall spatial brain patterns of AD participants were significantly different from the MCI participants, measuring the mean Pearson correlation of each patient's brain map with all other patients. The AD participants had mean correlations which were not significantly different from the MCI participants both at P-value > 0.05.

Demographic and Behavioral Analysis

The demographic (age, sex, education) and clinical data (Mini-Mental State Examination and MoCA scores) were analyzed using the statistical package for the social sciences (SPSS) software. Mean and SDs were computed for all continuous variables. The Shapiro-Wilk test, as well as homogeneity of variance test, was used to assess the normality of each continuous variable. If the variable showed significant deviations from normality on either test, then the nonparametric Mann-Whitney U test was utilized to test for significance, otherwise t tests were performed. Categorical variables (eg, sex, cardiovascular risk factors) were assessed for significance with the χ^2 test of independence.

RESULTS

Demographic Characteristics

Seventeen participants (mean age = 72.9; mean years of education = 15.4; female, n = 14, mean MMSE = 27.0, mean baseline MoCA = 23.1) were recruited from the St. Michael's Hospital Memory Disorders Clinic and from advertisements in the community. Separate demographic information is provided for participants with early AD and MCI (Table 1). Mean and SD were computed for all continuous variables. Categorical variables were assessed for significance with the χ^2 test of independence.

Brain Activation During Recently-heard and Long-known Music

For the recently heard—fixation contrast, our analysis revealed significant positive activation in multiple regions, specifically in the frontal, temporal, and subcortical brain areas (Fig. 1, middle row, in red). The frontal lobes showed significant right-sided activation in the inferior frontal gyrus (IFG) as well as the precentral gyrus. Significant bilateral positive activations were found in the temporal lobes, with greatest activation in the superior temporal gyrus (STG) followed by the medial temporal lobes and the temporal poles. Significant negative activations were found in the frontal regions only (Fig. 1, middle row, in blue). Frontal

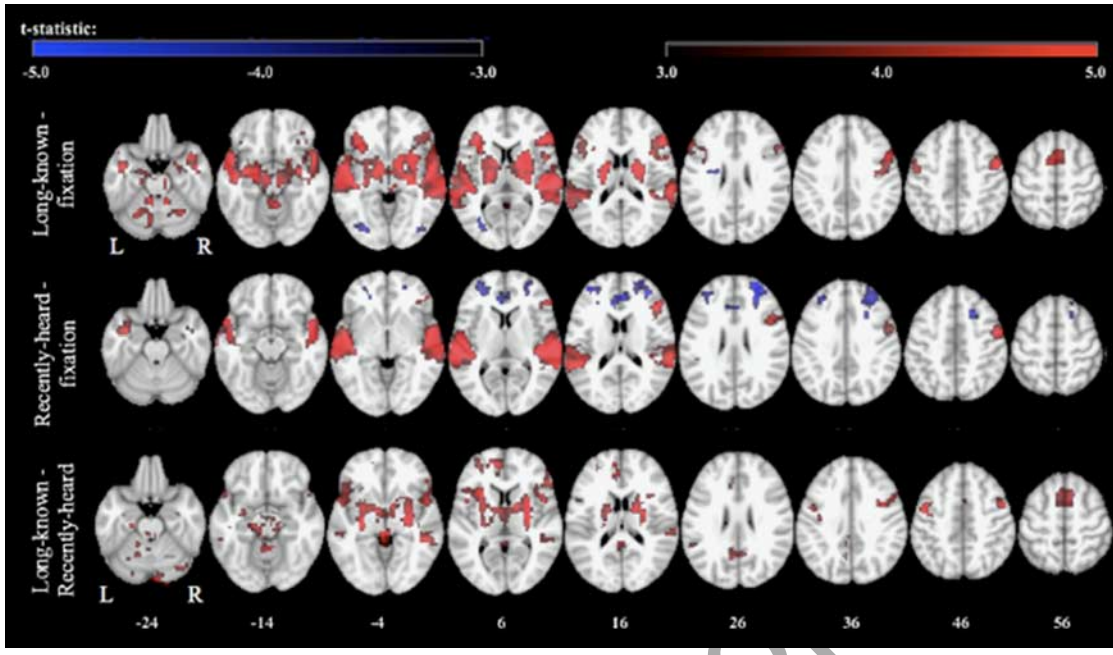

FIGURE 1. Brain activity associated with long-known and recently-heard music listening. One sample *t* test activation maps showing areas of significant group-level activation associated with long-known music listening (top row) and recently-heard music listening (middle row) relative to fixation. A direct comparison (bottom row) shows areas of greater activation (red) during long-known music listening compared with recently-heard music listening.

deactivations were found in the dorsolateral prefrontal cortex (PFC) (Brodmann area 46), extending slightly into the medial PFC (Brodmann area 9/10) as well as the anterior cingulate.

For the fMRI data, analysis of the long known—fixation contrast revealed significant positive bilateral activations in multiple brain regions (Fig. 1, top row, in red). Frontal activations included the premotor areas such as the SMA and precentral gyri, as well as inferior frontal IFG. The IFG activations extended into subcortical areas such as the anterior insula, putamen, pallidum, anterior thalamus; as well as medial temporal lobe structures such as the hippocampus, parahippocampal gyri, and amygdala. However, of all the temporal areas, the STG had greatest activation, followed by the MTG and extending into inferior temporal regions. Other significant areas of activations include the bilateral cerebellum. There was limited evidence of hemispheric lateralization, although, the right precentral gyrus had more spatially extensive activation than the left precentral gyrus. Significant negative activation (Fig. 1, top row, in blue) was found in the bilateral superior and inferior occipital areas.

Long-known music listening relative to recently-heard music (Fig. 1, bottom row) showed greater task-positive activation in several brain regions including frontal, temporal, parietal, and subcortical areas. Specifically, greater frontal activation was found bilaterally in motor regions such as the SMA and precentral gyri, as well as the IFG. In addition, the IFG activation extended bilaterally into subcortical regions, such as the anterior insula, putamen, pallidum, and anterior thalamus. In the temporal lobes, there was bilateral STG, MTG, and temporal pole activation, however, activation was mostly lateralized to the right for the STG and MTG. In the parietal lobe, the precuneus was preferentially bilaterally activated during long-known music listening. Finally, greater positive left-sided activation was found in the frontal areas such as the medial PFC (medial parts of Brodmann area 10), a small cluster is the dorsolateral PFC (lateral part of Brodmann area 10/46) and anterior cingulate; and in medial temporal areas such as the amygdala, hippocampus, and parahippocampal gyrus.

DISCUSSION

This study presents one of the few investigations of the neural correlates of musical memory in patients with AD or MCI to the best of our knowledge, obtained by exposing subjects to both long-known and recently-heard music. We predicted that exposure to long-known music would be associated with more widespread brain activation relative to recently-heard music, particularly in brain regions involved in emotion processing, given that it is more likely to evoke an emotional response. We also predicted that brain activations specific to long-known music would correspond to brain regions minimally affected by AD pathology as indicated by prior research.[5]

Our study corroborated prior work by Plailly et al,[14] similarly showing lateralization to the left hemisphere and demonstrating activation of the PFC, precuneus, and hippocampus during exposure to long-known music. In addition, our findings are consistent with that of Slattery et al[7] who found deficits in musical episodic memory correlated with abnormal activation of the precuneus. Our findings are also consistent with the work of King et al[6] who similarly found exposure to preferred music associated with activation of the SMA. However, there was much more activation in subcortical brain regions in our sample relative to these studies. Similarly, our study demonstrated more widespread activation of frontal, temporal, and subcortical brain regions following exposure to recently-heard music.

Participants exposed to long-known music had uniformly increased activation compared with recently-heard music. More specifically, areas showing increased activation included the medial PFC, the precuneus, anterior insula, basal ganglia, hippocampus, amygdala, and cerebellum. The medial PFC has been identified in prior studies as a hub for linking music with autobiographical memory[15] and, in conjunction with the anterior cingulate,[16] has been shown to regulate limbic regions involved in emotional response to music. The precuneus may additionally play an important role in autobiographical memory,[17] along with the cerebellum.[18] As predicted, these brain regions are minimally affected by AD pathology until the latter stages of the disease,[3,5] providing a putative explanation for the preservation of musical memory in patients with AD, whereas the regions associated with memory networks for recently-heard music did not extend into regions more spared by the disease biomarkers.

Clinical studies using music-based interventions in patients with AD have shown promise.[2] There are many possible mechanisms through which music may enhance memory function in general, including through its effects on mood and anxiety symptoms[19] and also by increased neurogenesis and synaptic plasticity.[20,21] Our research suggests that long-known music, in addition to activating brain regions associated with music exposure, may lead to increased activation of brain regions involved in the retrieval of autobiographical memory and associated emotional responses. This increased brain activation provides a potential mechanism by which musical memory is preserved. Moreover, it is possible that repeated activation of such brain regions may lead to improvements in overall memory. Though studies to date have been limited, Irish et al[22] measured changes in autobiographical memory associated with exposure to music versus silence in a cohort of patients with AD and healthy controls. They found a significant improvement in autobiographical memory scores in AD subjects exposed to music relative to the control condition. However, the music was not personally selected and there was no imaging to validate the neural mechanisms underlying the improved autobiographical memory scores.

Though the results of our study are of great interest and provide evidence of the neural mechanisms underlying preservation of musical memory in a cognitively impaired population, there are some limitations that should be pointed out. First, the sample size was relatively small, including only 17 subjects. Second, subjects had different levels of musical experience which may have confounded the results. Third, we combined patients with mild AD and patients with MCI, disorders that may have a different anatomic basis, though subanalyses of overall spatial brain patterns did not reveal any differences between participants with MCI and AD. Finally, the results are cross-sectional in nature and therefore we are unable to comment on the impact of long-known music exposure on progression of cognitive decline over time.

Despite the above-mentioned limitations, our study suggests that exposure to preferred long-known music activates brain regions involved in the retrieval of autobiographical memory and associated emotional responses above and beyond a short-term musical memory network formed by exposure to newly-heard music 60 minutes before scanning. This may provide an explanation for why musical memory is preserved in AD. Future studies in cognitively impaired populations are required to validate these findings and to further explore whether or not repeated exposure to long-known music may have therapeutic benefit in patients with cognitive disorders.

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