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Music Recognition in Frontotemporal Lobar Degeneration and Alzheimer Disease

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Abstract

Objective—To compare music recognition in patients with frontotemporal dementia, semantic dementia, Alzheimer disease, and controls and to evaluate the relationship between music recognition and brain volume.

Background—Recognition of familiar music depends on several levels of processing. There are few studies about how patients with dementia recognize familiar music.

Methods—Subjects were administered tasks that assess pitch and melody discrimination, detection of pitch errors in familiar melodies, and naming of familiar melodies.

Results—There were no group differences on pitch and melody discrimination tasks. However, patients with semantic dementia had considerable difficulty naming familiar melodies and also scored the lowest when asked to identify pitch errors in the same melodies. Naming familiar melodies, but not other music tasks, was strongly related to measures of semantic memory. Voxel-based morphometry analysis of brain MRI showed that difficulty in naming songs was associated with the bilateral temporal lobes and inferior frontal gyrus, whereas difficulty in identifying pitch errors in familiar melodies correlated with primarily the right temporal lobe.

Conclusions—The results support a view that the anterior temporal lobes play a role in familiar melody recognition, and that musical functions are affected differentially across forms of dementia.

Keywords

Pitch; Melody; temporal lobe; auditory perception

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INTRODUCTION

Perhaps one of the most common cognitive processes triggered by music is the evaluation of whether a melody or musical excerpt is familiar. Recognition of familiar music depends on several levels of processing, including basic perceptual processes that extract pitch and rhythm, as well as higher-order processes that associate sequences of pitches and temporal patterns with long-term memories for those patterns [1]. Considerable evidence has amassed that both the temporal and frontal lobes support tonal processing in humans [2].

Neuropsychological studies of individuals with brain damage following stroke or surgical removal of brain tissue have helped dissociate musical processes in terms of their underlying neural substrates, and have supported a modular view of musical functions [3]. While it is generally accepted that damage to the temporal lobes affects the processing of melodies [2, 4], the observed dependencies of perceptual and associative processes on sub-regions of the temporal lobes in the two hemispheres are variable across studies. For example, in a sample of patients with damage to either one or both hemispheres [5], recognition of either newly learned melodies or familiar folk melodies was significantly impaired in left hemisphere patients. These patients were able to detect notes in melodies that violated the established key but were impaired in detecting more subtle melodic violations. Right hemisphere patients were impaired on all types of melody violations, but recognition and naming of familiar melodies and recognition of newly learned melodies remained intact. Together, these results suggest a dissociation between perceptual and associative aspects of melody perception. The right anterior temporal lobe may enable melodic contexts to influence the perception of individual notes[6], though another large scale patient study has found that the posterior superior temporal gyrus needs to be damaged for melody perception processes to be affected[7].

A neuropsychological approach that complements the study of patients with selective music processing deficits resulting from stroke or surgical removal of brain tissue is the study of patients who have been diagnosed with various forms of dementia. Here we focus on neurodegenerative disease patients with frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD). FTLD is divided into three clinical subgroups [8], including frontotemporal dementia (FTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA). SD is characterized by a progressive loss of semantic memory and atrophy of the temporal lobes (including the temporal pole, inferior and middle temporal gyri), amygdala, the anterior portions of the parahippocampal gyrus, and the fusiform gyrus [9-13]. Patients with FTD have changes in interpersonal and personal conduct, emotional blunting, and early loss of insight that is associated with atrophy in the orbital frontal, insular, and anterior cingulate regions [9]. Finally, patients with progressive non-fluent aphasia (PNFA) are characterized by effortful and agrammatic speech[14, 15].

Only a few studies have evaluated music abilities in FTLD patients. Two studies describe a new, compulsive interest in music in two patients with FTD and one with SD[16, 17].. The new compulsion is noteworthy because both patients previously disliked the genre of music that became the focus of the compulsion. Another study [18] discussed the emergence of a new interest in composing music in one patient with progressive aphasia and another with FTD. They concluded that the enhancement of music creativity was most common in patients with left anterior temporal damage. Recent case studies found only mildly worse recognition of familiar melodies in both a musically untrained [19] and a highly musically trained SD patient [20]. The latter study examined a variety of forms of musical knowledge and found different patterns of performance in the AD and SD patient. Most notably, the SD patient was severely impaired in naming of familiar melodies and instrument sounds, in the recognition of instrument sounds if they were not associated with instrument pictures, and in

the recognition of emotional intent in music. By contrast, the AD patient showed relatively spared instrument sound and emotion recognition, but experienced difficulty in retrieving specific knowledge about famous musical compositions. A recent review also concluded that the recognition of familiar melodies is impaired in individuals with AD[21]. However, it is important to keep in mind that recognition was assessed by different methods in these studies, and there was a range of impairment described.

Apart from the case studies reviewed above, no studies have yet applied a systematic assessment of music recognition in patients with FTLD or compared groups of FTLD and AD patients. The purpose of this study was to compare the recognition of music in patients with FTLD and AD. Within the FTLD group, we focused particularly on SD, a subtype of FTLD that is associated with a semantic memory impairment. Patients with SD are impaired in recognizing both verbal and non-verbal information such as objects, environmental sounds, famous faces and voices, scents, and tastes[22, 23]. AD patients are known to have semantic impairment [24] but to a lesser degree than SD [25]. Moreover, there is evidence that certain musical faculties, in particular the recognition of familiar music, are preserved in patients with AD[26, 27]. Although a deficit in semantic memory is not common in FTD, we included FTD patients because of the presence of frontal and temporal cortex atrophy and the paucity of studies investigating music recognition in this subgroup.

In the current study we focused on the recognition of both familiar and unfamiliar melodies.. We further examined brain/behavior relationships using voxel-based morphometry (VBM). Given the previous patient studies indicating temporal lobe involvement in melody judgments and recognition[5-7] as well as neuroimaging studies indicating anterior temporal lobe engagement during music familiarity judgments[28, 29] together with observations of increased atrophy of temporal pole areas in SD[10, 11, 13], we predicted that performance on our music recognition tasks would correlate with VBM measures of atrophy in the anterior temporal lobe.

MATERIALS AND METHODS

Subjects

The patients were recruited from the University of California, San Francisco (UCSF) Memory and Aging Center, a tertiary dementia clinic and research program. Clinical diagnosis was determined after a detailed clinical history, neurological examination, a one-hour neuropsychological battery [30], laboratory screening, and brain MRI (which was used to exclude patients with stroke, tumor, or other brain abnormalities). Patients with FTD met Neary criteria [8] (n=11) and had early decline in interpersonal and personal conduct, emotional blunting, and early loss of insight. Patients with SD met Neary criteria [8] (n=20) and had a progressive, fluent language disorder characterized by severe anomia and loss of semantic memory. Patients with probable AD (n=12) met NINCDS-ADRDA criteria [31].

We selected patients in the mild to moderate stages of dementia, as defined by a Mini-Mental State Examination (MMSE) [32] score greater than 15 or a Clinical Dementia Rating (CDR) [33] of less than two. Based on previous experience, we used either the MMSE or CDR for inclusion in the study. We expected the patients with SD to score lower on the MMSE because of the dependence on language and patients with FTD to have more functional impairments on the CDR [34].

Healthy controls (n=17) were recruited from the community and underwent an evaluation identical to the patients. None of the controls showed evidence of impairment on neuropsychological testing or had a history of a neurological or psychiatric disorder.

Demographic information (i.e., age and education) and years of music lessons were compiled. Professional musicians were excluded from this analysis. None of the subjects had a history of hearing impairment or hearing aid use. All participants (or surrogates) provided informed consent obtained according to the Declaration of Helsinki, and the study was approved by the UCSF committee on human research.

Neuropsychological Battery

All subjects were administered a comprehensive neuropsychological battery that measures multiple domains of cognition. Memory was evaluated using the 10-minute delayed recall trial of the California Verbal Learning Test – Mental Status (CVLT-MS) [35] and the Wechsler Memory Scale – Visual Reproductions [36]. The longest correct backward digit span and spatial span on the WAIS-III Digit and Spatial Span subtests [37] were used as measures of working memory. Executive function was assessed using tests from the Delis-Kaplan Executive Function System (D-KEFS) [38]: Trailmaking (number-letter condition, scaled score), Stroop (Interference condition, scaled score), and Design fluency (switching condition, scaled score). Measures of verbal fluency included letter fluency (FAS, number correct in 3 minutes) and animals (number correct in 1 minute). Language was assessed using a 15-item Boston Naming Test [39], the WAIS-III Information subtest [37], 16 items from the Peabody Picture Vocabulary Test – Revised [40], and sentence comprehension subtest from the Curtiss-Yamade Comprehensive Language Evaluation-Receptive (CYCLE-R) [41]. Patients with SD were also administered the Pyramid and Palm Trees test (pictures) [42] to evaluate semantic associations. The copy trial of the modified Rey-Osterrieth figure [30] and the Number Location condition from the Visual Object Spatial Perception battery (VOSP) [43] were used to assess visuospatial abilities.

Music Cognition Tasks

Overall, the music battery evaluated the ability to discriminate two tones and process both familiar and unfamiliar melodies. The pitch discrimination and familiar melody tasks were designed for the present study, whereas the melody discrimination task was from the *Montreal Battery for the Evaluation of Amusia* (MBEA) [44]. The stimuli for the newly designed tasks were generated using the grand piano patch of a Roland Canvas sound module (Roland Canvas SC-8850) and stored as wav files. All tasks were administered on a laptop computer with two portable speakers with the volume adjusted to a comfortable loudness level for each subject in a quiet, free field room.

Pitch Discrimination—The pitch discrimination task was designed as a control task for the two melody tasks (to assure that the participants were not making errors based on global pitch processing deficits) and was not intended to investigate pitch discrimination thresholds. This task required subjects to determine whether two successive tones (separated by a 1 s inter-stimulus interval) were the same or different. The tones ranged from G5-C4 and were 1 s in length. Ten pitch pairs differed by 3-8 semitones, and 10 were the same two tones. Following two practice examples, 20 pitch pairs were randomly presented.

Unfamiliar Melody Discrimination—The melody discrimination task (Task 1 - Scale from the MBEA) [44] was used to assess the ability to discriminate two melodies that differed by one pitch. We selected Task 1 from the MBEA because it required subjects to detect a single key-violating pitch change, which is similar to the familiar melody task, and testing time limited the administration of the complete MBEA battery. Subjects were asked to listen to 30 pairs of unfamiliar melodies (ranging in length from 3.8 to 6.4 seconds per melody) and determine if they were the same or different (15 trials of each). The audio file was paused (for up to 10 seconds) for subject response. In the different trials, the second melody was modified by introducing a key-violating pitch change that deviated from the original

tone by an average of 4.3 semitones (range = 3-7) and preserved the contour (shape) of the melody. Half of the pitch substitutions occurred in the first half of the melody, while the remaining occurred in the second half.

Detection of Pitch Errors in Familiar Melodies—The pitch error detection task was designed to evaluate tonal knowledge about familiar melodies by asking subjects to detect a wrong note in excerpts of familiar melodies. This task was designed considering previous studies that used altered versions to assess tonal knowledge about familiar melodies [45, 46]. Twelve highly familiar melodies were selected from American popular music songbooks [47, 48] and expected to be easily recognizable to individuals who are familiar with United States culture. (Appendix A) All of the selected familiar songs were originally written with lyrics, but only the melody was reproduced (monophonically on an electronic keyboard) with an effort to preserve the original tempo, rhythm, and style (including accents, phrasing, loudness of notes). The melodic excerpt included the portion of the melody in which the song title was a part of the song text, although only the melody was reproduced. The familiar melodies had an average length of 17 seconds (range = 13-21), and the octave range was A3 to G5.

Subjects were instructed that some of the melodies would have a wrong note and were asked to determine if the excerpt was “correct” or “incorrect”. Two-thirds of the melodies included an alteration of a single pitch. For the altered melodies, pitch errors either preserved (key-preserving) or violated (key-violating) the key (tonality) of the melody. There were four trials for each of the three conditions. The pitch substitutions deviated from the original pitch by 1-3 semitones and were at least 2 steps away in the circle of fifths from the original key. After selecting the key, a pitch that either preserved or violated the key was selected. All pitch errors preserved the contour of the original melody. (Figure 1 provides an example of a melody with each type of error.) All pitch errors preserved the contour of the melody and occurred on a prominent beat (non passing tones). None occurred in the first or last measure of the excerpt.

Familiar Melody Title Recall—After completing each pitch error trial, subjects were asked to provide the title of the familiar melody excerpt. The song titles were scored as correct if all content words of the title were provided (*e.g.*, ignoring accuracy of prepositions or articles). If the subject did not provide a correct spontaneous title, four written titles were presented on a card. The multiple choice responses included the correct title and three foils: 1) an invented but semantically related title, 2) a real and semantically unrelated song title and 3) an invented and semantically unrelated title.

Statistical Methods for Behavioral Data

We compared diagnostic groups using one-way analysis of variance (ANOVA) to examine possible group differences in the demographic and neuropsychological data. *Post hoc* analyses were conducted using Tukey’s method for multiple comparisons using SPSS (version 16.0 for Windows, SPSS Inc, Chicago IL). The non-parametric Kruskal-Wallis rank test was used with the non-normally distributed experimental data (pitch discrimination, familiar melody title recall, and familiar melody title recognition). The alpha level was set at 0.05. For significant group differences, we used the Fisher exact test to examine pair-wise group differences. We examined the relationship between experimental and neuropsychological measures using scatter plots and Pearson product moment partial correlations controlling for MMSE. We controlled for the MMSE in our correlation analysis because we were interested in evaluating the correlation between the music tasks and neuropsychological tests that is *independent* of dementia severity.

Voxel-based Morphometry Analysis Methods

We examined the relationship between performance on the music tasks and MRI gray matter volume by collapsing across subject groups and using voxel-based morphometry (VBM) regression methods, similar to other studies [49, 50]. Investigation of this relationship across study groups increased the statistical power and variability in the regression analysis. High definition T1-weighted whole-brain MRI was obtained from a subset of participants within six months from clinical testing. VBM analyses were performed on 13 controls and 23 patients (7 AD, 6 FTD, and 10 SD) with a mean age of 63.6 years (21 males and 15 females). The scans were acquired on a 1.5T Magnetom VISION system (Siemens, Iselin, NJ). A volumetric magnetization prepared rapid gradient-echo MRI (MPRG, TR/TE/TI = 10/4/300 milliseconds) was used to obtain T1-weighted images of the entire brain, 15-degree flip angle, coronal orientation perpendicular to the double spin-echo sequence, 1.0 × 1.0 mm in-plane resolution and 1.5 mm slab thickness.

VBM analysis included two steps: spatial preprocessing (normalization, segmentation, Jacobian modulation and smoothing) and statistical analysis. Both steps were implemented in the SPM2 software package (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 6.5.1 (MathWorks, Natick, MA). MRI images were pre-processed using the optimized technique to improve spatial normalization and segmentation of gray matter[51]. An ad hoc template and *a priori* images were created from 30 age- and gender-matched healthy controls, and images were segmented, normalized, modulated and finally smoothed with a 12 mm FWHM isotropic Gaussian kernel.

Statistical analysis used the “covariate-only” model in SPM2, and all images were entered as a single group. The scores of the music cognition tasks were entered as independent covariates, and the relationship between gray matter volume and performance on the music tasks was evaluated. Total intracranial volume, age and gender were used as nuisance variables. To identify brain regions associated with each task, we investigated the effect of each variable separately. Four design matrices were constructed in which only one of the following covariates was entered: pitch discrimination scores, melody discrimination scores, detection of pitch errors in familiar melodies scores, and familiar melody title recall scores. A whole brain analysis was conducted, and the alpha level was set at $p<0.001$ uncorrected within a priori regions of interest defined as the bilateral temporal lobe and bilateral inferior frontal gyrus based on the literature reviewed in the introduction. A threshold of $p<0.05$ FWE corrected was considered for regions outside the a priori regions.

RESULTS

Demographic and Neuropsychological Test Results

A summary of the demographic data are found in Table 1. Age, years of education, and years of music lessons did not differ among groups (all $p>0.05$). All patients scored significantly below controls on the CDR-sum of boxes ($p<0.001$).

The neuropsychological testing results are found in Table 2. There were group differences on all neuropsychological tasks (all $p<0.05$). As expected, the neuropsychological test results are similar to other published studies [30, 52]. On the MMSE, the patients with SD and AD scored significantly lower than controls, while FTD patients scored similarly to controls. The patients with AD and FTD, but not SD, scored below controls on the digit span task, and only the patients with AD scored below controls on the spatial span task. All patient groups scored below controls on tests of verbal and visual memory. Similarly, all patient groups scored below controls on the tests of generation (i.e., letter and category fluency). On tests of executive function, all patient groups scored below controls on Trailmaking and

Design fluency, but only AD and SD patients scored below controls on Stroop Interference. On the visuospatial tasks, only AD patients scored below controls on the modified figure copy and VOSP number location. Both SD and AD patients, but not FTD, scored below controls on the Boston Naming Test. All patient groups scored below controls on the Information subtest. In contrast, only SD patients scored below controls on the PPVT-R, and only the AD patients scored below controls on the CYCLE sentence comprehension.

Pitch Discrimination Results

As expected, there were no group differences on pitch discrimination (Kruskal-Wallis test, X^2=5.09, df 3, p=0.16) (Table 3). All but one control scored 20/20 correct. Because of near-ceiling performance on this task, we did not perform the correlation analysis. .

Melody Discrimination Results

There were no group differences on melody discrimination (Kruskal-Wallis test, X^2=2.58, df 3, p=0.46). (Table 3) The controls scored a mean of 26 out of 30 (range=22-29, SD=2.4), which is similar to the normative sample of 160 healthy adults reported by Peretz and colleagues (mean=27, SD=2.3) [44]. Peretz *et al.* [44] use a score of 22 as the cut-off between normal and impaired performance. In our sample, 33% of the patients across different diagnostic groups (2 AD, 4 FTD, 7 SD) and one control scored below 23. Performance on melody discrimination did not correlate with years of music lessons (r=0.03, p=0.85). After controlling for MMSE, there were no significant correlations between melody recognition or any neuropsychological measures (all p>0.05).

Familiar Melody Pitch Error Detection Results

Figure 2 shows the results on the familiar melody error detection task. Controls had an average accuracy of 91%. There were group differences in overall accuracy (F(3,51)=3.39, p=0.007). *Post hoc* analyses showed that only SD patients had lower scores when compared with controls, AD and FTD (p<0.001), but there was a trend for AD and FTD patients to score lower than controls. Table 3 summarizes the performance on each of the three trial types for this task. As expected, all groups scored higher on the key-violating trials when compared to the key-preserving trials. Notably, the SD patients also showed this pattern despite low overall scores.

Performance on the pitch error task did not correlate with years of music lessons (r^2=0.19, p=0.19). After controlling for MMSE, there were no significant correlations between pitch error detection and any neuropsychological measures (all p>0.05).

Familiar Tune Title Recall Results

Figure 3 summarizes the title recall and recognition results. Controls provided correct titles for 81% of the familiar melodies. There were group differences in performance (Kruskal-Wallis test, X^2=12.12, df 3, p=0.007), and all patient groups recalled significantly fewer song titles than controls (all p<0.04). Patients with SD also recalled fewer titles than patients with AD and FTD (both p<0.001).

After controlling for MMSE, the recall of song titles was significantly correlated with scores on the Boston Naming Test (r=0.78, p=0.003), WAIS-III Information (r=0.86, p<0.001), PPVT-R (r=0.87, p<0.001), and animal fluency (r=0.62, p=0.03) but none of the other neuropsychological tests. Naming familiar songs did not correlate with years of music lessons (r=0.01, p=0.95). These results suggest that naming familiar melodies depends on cognitive processes that are indexed by verbal tests of semantic knowledge.

Familiar Melody Title Recognition Results

When given four written song titles in a multiple choice format, controls performed at ceiling and obtained a recognition score of 99.5% correct (*i.e.,* proportion of spontaneously named titles plus correct multiple choice). (Figure 3) There were significant group differences on title recognition (Kruskal-Wallis test, X^2=30.71, df 3, p<0.0001), and only SD patients scored significantly lower than controls (p<0.001); SD patients also scored lower than both FTD and AD patients (both p<0.0001) (Figure 3). Even when given four written title choices, the SD patients identified only 62% of the correct titles. When SD patients incorrectly selected the title, 43% were other familiar song titles, 41% were semantically-related (but novel) titles, and 16% were invented song titles.

Voxel-Based Morphometry Results

The results of each analysis are reported separately. No correlations with pitch discrimination scores were found. The results of the VBM analyses are found in Figure 4 (A-C) and Table 4.

Melody Discrimination—Scores on the melody discrimination task correlated with right inferior temporal cortex and right temporal pole (p<0.001, uncorrected) (Figure 4A, Table 4). The bilateral orbito-frontal cortex also showed an effect at the same threshold and are reported for completeness.

Detection of Pitch Errors in Familiar Melodies—The ability to detect pitch errors in familiar melodies correlated with right temporal lobe, including the inferior and superior temporal gyrus and temporal pole (p<0.001, uncorrected) (Figure 4B, Table 4).

Familiar Melody Title Recall—The ability to generate titles for familiar melodies correlated with large regions in the bilateral temporal lobes, right frontal cortex and several subcortical structures. Within the left temporal cortex, naming familiar melodies correlated with lateral and medial temporal cortex, including the hippocampus, temporal pole, and inferior and middle temporal gyrus. Additional correlations between naming and brain volume were found in the right hemisphere including the right inferior frontal gyrus (pars triangularis), inferior temporal gyrus and hippocampus (p<0.001, uncorrected). (Figure 4C, Table 4). Subcortical regions are reported for completeness, but they were not within our a priori regions of interest and did not reach a corrected level of significance.

DISCUSSION

Overall, the results indicate that patients with neurodegenerative diseases and healthy controls vary in their ability to identify music as familiar. The main finding is that patients with SD performed substantially worse than AD and FTD patients and controls when naming familiar songs and were also worse than controls at detecting pitch errors in the same familiar songs. Although both AD and FTD patients generated fewer spontaneous titles for the familiar melodies than did controls, these patients were able to select the correct title in a multiple choice format. The patients with SD improved with multiple choice title format but not to the performance level of the other dementia groups or controls. VBM analyses of brain MRI in a subset of participants indicated that naming familiar songs correlated with the volume of the left temporal cortex (including left inferior and middle temporal gyri and temporal pole) but also right inferior temporal gyrus and right inferior frontal gyrus. In contrast, difficulty with detecting pitch errors in familiar melodies was correlated with right temporal lobe structures, including the right inferior and superior temporal gyri and the temporal pole. Interestingly, the ability to identify pitch errors in familiar melodies did not correlate with any neuropsychological tests, whereas naming

familiar melodies only correlated with tasks involving object naming and verbal semantic knowledge. Finally, there were no group differences on the pitch or melody discrimination tasks, suggesting that all groups were able to process basic pitch and novel melodic information.

The ability to name (i.e., generate a verbal title) for familiar music is not yet well understood. Song titles can be arbitrary labels, include a portion of the song lyrics, or refer to semantic content of a song. Deficits in naming familiar melodies have been associated with left-sided or bilateral damage. In an early study, Shankweiler [53] demonstrated that patients with either right or left temporal lobectomies had difficulty naming familiar songs compared with controls. Eustache and colleagues [54] also found that a patient with a left anterior temporal and left parietal stroke had difficulty naming familiar songs, but was able to improve performance to 90% with multiple choice titles. In addition, Ayotte *et al.* [5] found that patients with left-sided and bilateral MCA ruptured aneurysms named fewer songs than did unilateral right patients.

Few studies have assessed familiar melody naming in patients with neurodegenerative diseases. Omar and colleagues [20] recently described a professional musician with SD who had a severe impairment in naming familiar melodies, music symbols, and instrument sounds and pictures.. However, in contrast to our findings, recognition of familiar melodies in this musician with SD (as assessed by a famous melody matching task) remained relatively intact. The SD patients in our study had considerable difficulty naming familiar melodies, but they also performed the lowest on detecting pitch errors in familiar melodies,. In further contrast to our findings, the professional musician with AD described by Omar and colleagues[20] was impaired in both the naming and recognition of familiar melodies. However, our study excluded professional musicians and used different tasks to assess familiar melody recognition. For example, we also used a multiple choice format for title recall. Although the FTD and AD patients spontaneously named fewer melodies, they were able to select the correct title from a multiple choice format. SD patients also improved with multiple choice titles but not to the performance level of the FTD, AD or controls.

No studies to date have used brain imaging methods to evaluate the brain networks involved in generating a title for a familiar song. The MRI analysis in our study suggested that difficulty in naming familiar songs correlated primarily with left temporal cortex (including left inferior and middle temporal gyri and temporal pole) but also right inferior temporal gyrus and right inferior frontal gyrus. These findings help focus attention on a possible brain network involving bilateral temporal lobe and right frontal cortex for generating a title for a familiar melody, and in particular, naming familiar songs that have a text. Similar to Ayotte and colleagues[5], naming songs also correlated with verbal tests of object naming and semantic memory but not other neuropsychological tests. Naming familiar songs may be similar to generating names for other types of information in terms of cognitive processing and brain regions involved. However in the current study, we cannot isolate the contribution of verbal and non-verbal components when generating a song title because we utilized familiar songs that had an associated with a song text (even though we only presented the melody). Recent studies have attempted to address this issue with more specialized methods for examining the verbal and music components of songs [55, 56].

Recognition of familiar melodies can also been evaluated using other methods, such as with pitch error detection tasks. Healthy adults maintain relatively precise knowledge about familiar melodies. In particular, adults retain exact knowledge about the intervals of familiar melodies and are able to detect pitch or rhythmic errors in familiar melodies with high accuracy.[57-59] Several researchers [3, 60-62]propose that recognition of a familiar melody is dependent on a series of cognitive processes that connect an auditory mental representation

with a “musical lexicon” that represents specific, known melodies. Detecting pitch errors is one method for assessing familiarity and knowledge about a familiar melody. Correct judgments about the accuracy of a melody can be achieved only if knowledge about specific intervals of the familiar melody is preserved.

With regards to detecting pitch errors in familiar melodies, several studies have documented an association between right hemisphere damage and difficulty on this task. For example, Shapiro and colleagues [63] found that patients with right-hemisphere lesions performed worse than patients with left-hemisphere lesions when asked to identify pitch errors in familiar melodies. In addition, patients with lesions of the temporal lobe anterior to Heschl’s gyrus exhibit less facilitation of pitch intonation judgments by a melodic context [6]. Using positron-emission tomography (PET) imaging with healthy adults, Satoh and colleagues [29] found activation of bilateral superior/inferior parietal lobules, precuneus, and lateral frontal cortex when asked to identify an altered familiar melody, however with changes in *both* pitch and rhythm. The findings from our study suggest that difficulty in detecting pitch errors correlated with atrophy in the right inferior and superior temporal gyrus and temporal pole. We did not find correlations with frontal or parietal regions that were seen in the PET study. However, there are differences between metabolic and structural imaging methods. One methodological issue to consider when comparing studies is that several authors use “naming” of a familiar melody to reflect familiar melody “recognition”. Data from the current study show different results for the naming of melodies and the recognition of pitch errors in familiar songs.

The inability to recognize familiar melodies (using different methods) has been associated with damage to several brain regions, most commonly bilateral auditory cortex 55-58, bilateral anterior temporal [64], and a combination of frontal and temporal lobes [1]. Reports of patients with difficulty recognizing familiar melodies, originate in the late nineteenth century [65]. Peretz and colleagues[66-68] described three patients with bilateral damage to the auditory cortex (CN, GL, IR) who lost the ability to recognize familiar music despite relatively intact processing of familiar environmental sounds. Using PET imaging with healthy adults, Platel and colleagues [28] administered a melody familiarity judgment task and found activation of the left anterior portion of the temporal gyrus (middle and superior), bilateral frontal cortex (medial and orbital), and left angular gyrus. Peretz and colleagues [60] argue that right superior temporal sulcus, in particular, is important for making familiar versus unfamiliar melody judgments. An fMRI study that used popular music to study music-evoked autobiographical memories found left-lateralized and stronger responses in medial and lateral prefrontal areas, the posterior superior temporal gyrus, middle temporal gyrus, and angular gyrus for excerpts from familiar songs than for excerpts from unfamiliar songs [69]. Thus, the neuroimaging data suggest that different brain structures are activated during different types of tasks involving familiar music and primarily involve temporal and frontal cortices. The differences between studies may reflect the different methods used to assess knowledge about familiar melodies (*e.g.*, familiarity judgment versus error detection).

Apart from a handful of case studies, few group studies have examined the recognition of familiar tunes in patients with dementia. A recent study [70] with 12 individuals with moderate to severe AD found considerable variability in their ability to detect pitch errors in familiar melodies. With regard to patients with SD, Hailstone and colleagues [19] argued that music knowledge is relatively preserved in SD patients after documenting a nonmusician who showed increased interest in popular music and was able to continue to sing/hum 25/40 familiar melodies; however, no other music tasks were administered. As discussed above, Omar and colleagues [20] found an impairment in naming familiar melodies, but recognition of familiar melodies (as assessed by a famous melody matching task) remained relatively intact in one musician with SD. In contrast, our data with 20 nonmusicians with SD suggest

a deficit in both naming familiar melodies and also detecting pitch errors in familiar melodies. Caution must be exercised when comparing case studies with group data and subjects with different backgrounds in music training.

At the level of more basic perceptual processes, the results suggest that there were no group differences in the ability to discriminate short, novel melody pairs that differed by one note. A deficit in the ability to discriminate unfamiliar melodies has been observed in patients with primarily right-sided damage. On the identical task used in our study, several authors found that patients with right-sided damage perform worse than left-sided damage[5, 7, 71, 72]. An fMRI experiment in which musically trained individuals made out-of-key or timbral deviation judgments while listening to a melody found modulation of activity in the right anterior temporal lobe [73], consistent with the observation in the present VBM analyses that subjects who had difficulty detecting pitch changes in novel melodies had atrophy in the right temporal pole.

In summary, music recognition is differentially affected in patients with SD, FTD, and AD. Patients with SD have disproportionate impairment when naming familiar melodies and were worse than AD or FTD patients in recognizing pitch errors in familiar melodies. Other studies document that patients with predominantly right-sided temporal lobe atrophy have deficits in the recognition of familiar people[22, 23, 74], person-specific knowledge [75], odors [76], and food[77]. The degree to which the right temporal lobe contributes to semantic processing is still a topic of debate [11, 78]. The overall body of patient evidence suggests that the detection of pitch errors in familiar melodies may be bilaterally distributed or perhaps rely somewhat more on the right hemisphere, while the naming of familiar melodies may rely on more left hemisphere networks. Studies of SD patients with differential patterns of atrophy across the two hemispheres may help further clarify the dissociation of recognition and naming processes associated with familiar music. Finally, standard tests of familiar music recognition should be done across studies.

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Appendix A: List of Familiar Melodies

Oh My Darling Clementine

Jingle Bells

For He’s a Jolly Good Fellow

Happy Birthday

I’ve Been Working on the Railroad

She’ll Be Comin’ Round the Mountain

My Country Tis of Thee

Amazing Grace

Let Me Call You Sweetheart

Oh Susanna

Oh When the Saints Go Marching In

You Are My Sunshine

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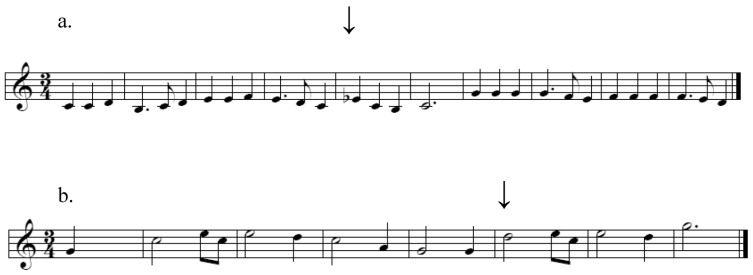

Figure 1.
Examples of Pitch Errors Used in Familiar Melody Pitch Error Detection Task.
a. Example of a key-violating pitch error in “My Country ‘Tis of Thee”. The E^{b} in measure 5 replaced the original note (F).
b. Example of key-preserving pitch error in “Amazing Grace”. The D in measure 6 replaced the original note (C).

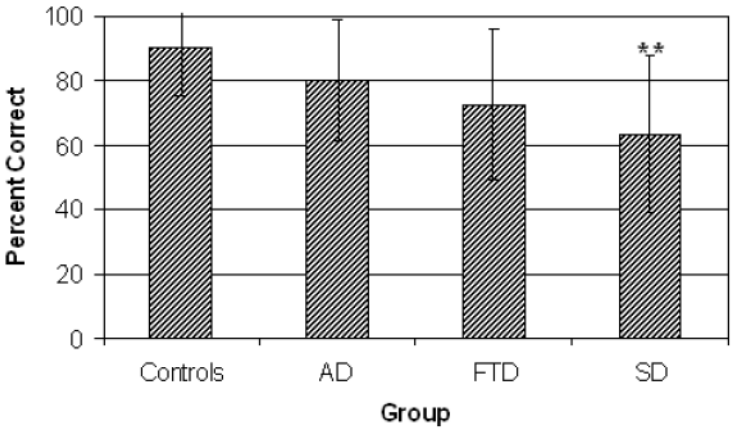

Figure 2.

Pitch Error Detection for Familiar Melodies. (Overall mean percent correct and standard deviation). In the bar graph, ** $p<0.0001$ compared with controls, AD and FTD. AD = Alzheimer disease, FTD = frontotemporal dementia, SD = semantic dementia

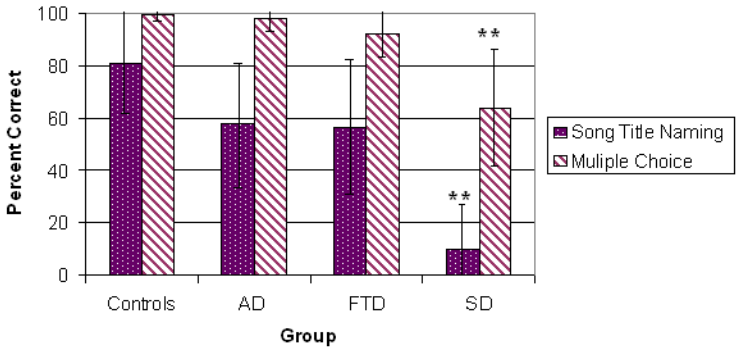

Figure 3.

Familiar Melody Title Naming and Multiple Choice (Mean percent correct and standard deviation). In the bar graph, ** $p<0.0001$ compared with controls, AD, and FTD. AD = Alzheimer disease, FTD = frontotemporal dementia, SD = semantic dementia

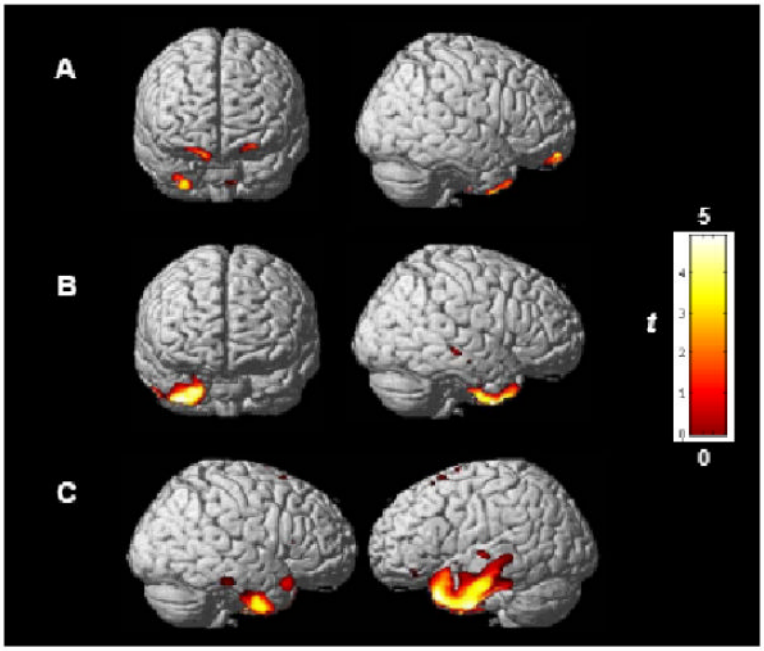

Figure 4.
Correlation of gray matter volume with performance on music tasks using voxel-based morphometry: (A) Correlation of gray matter volume with performance on the unfamiliar melody discrimination task. (B) Correlation of gray matter volume with performance on the familiar melody pitch error detection. (C) Correlation of gray matter volume with performance on familiar melody title recall.

Table 1

Demographics (Mean and standard deviation)

	Controls	AD	FTD	SD
N	**17**	**12**	**11**	**20**
Age (years)	66.3 (7.0)	65.3 (9.4)	59.8 (6.5)	66.2 (9.5)
Sex (men: women)	7:10	8:3	7:2	6:3
Education (years)	17.5 (2.2)	15.6 (2.9)	16.2 (2.9)	16.7 (3.0)
Music Lessons (years)	2.8 (3.9)	5.1 (5.2)	3.7 (5.3)	4.6 (5.8)
CDR – sum of boxes	0.1 (0.4)	5.3 (1.9)	6.1 (2.5)	4.2 (2.6)

AD = Alzheimer disease, FTD = frontotemporal dementia, SD = semantic dementia, CDR = Clinical Dementia Rating

Table 2

Neuropsychological Test Results (mean and standard deviation)

	Controls	AD	FTD	SD	*p* value
MMSE (30)	29.6 (0.8)	22.1 (5.1)*	26.3 (3.4)	23.2 (5.7)*	< 0.001
Working Memory					
Backward Digit Span (9)	5.7 (1.1)	3.4 (1.6)*	4.0 (1.5)*	4.8 (1.8)*	0.002
Backward Spatial Span (9)	4.8 (0.9)	2.4 (1.7)*	4.2 (1.8)	4.9 (1.2)	0.001
Verbal memory					
CVLT-MS - 10 min. recall (9)	7.2 (1.4)	0.9 (1.2)*	4.2 (3.3)*	1.9 (2.4)*	0.001
Visual memory					
Visual Reproductions – Delayed (17)	13.6 (3.7)	4.8 (2.6)*	8.6 (4.6)*	6.6 (3.2)*	<0.001
Executive					
DKEFS Trailmaking – Shifting (19)	11.9 (2.1)	2.7 (3.0)*	5.5 (3.9)*	6.9 (4.1)*	<0.001
DKEFS Stroop – Interference (19)	11.4 (1.5)	2.4 (3.1)*	6.9 (5.3)	5.3 (4.6)*	<0.001
DKEFS Designs – Switching (19)	12.5 (2.1)	7.2 (1.5)*	8.6 (3.9)*	8.7 (3.8)*	0.002
Visuospatial					
Rey-Osterrieth figure copy[1] (17)	16.1 (1.3)	9.45 (6.8)*	15.3 (1.8)	15.5 (1.3)	<0.001
VOSP Number Location (10)	9.5 (0.6)	4.9 (2.7)*	8.5 (1.0)	9.5 (1.0)	<0.001
Fluency					
Letter (FAS) (3 min.)	48.9 (9.2)	22.8 (14.2)*	27.6 (14.5)*	17.5 (8.5)*	<0.001
Category (Animals) (1 min.)	24.1 (4.3)	9.4 (5.4)*	12.0 (7.3)*	5.5 (4.1)*	<0.001
Language					
Boston Naming Test (15)	14.7 (0.6)	12.1 (3.4)*	12.5 (2.0)	3.0 (2.6)*	<0.001
WAIS-III Information (19)	15.1 (3.0)	9.7 (3.5)*	9.8 (3.3)*	3.9 (1.9)*	<0.001
PPVT-R Comprehension[2] (16)	15.8 (0.6)	14.3 (1.4)	14.6 (1.5)	5.7 (3.6)*	<0.001
CYCLE Sentence (10)	9.8 (0.4)	7.0 (2.8)	8.6 (2.2)	7.5 (2.1)	0.02
Pyramids and Palm Trees[3] (52)	--	--	--	36.1 (6.5)	NA

AD = Alzheimer disease, FTD = frontotemporal dementia, SD = semantic dementia, MMSE: Mini-Mental Status Examination, CVLT-MS: California Verbal Learning Test-Mental Status, VOSP: Visual Object and Space Perception Battery.

[1] Modified Rey-Osterreith figure copy;

[2] PPVT-R: Modified Peabody Picture Vocabulary Test – Revised;

[3] Pyramids and Palm Trees (pictures), chance = 26/52;

* different from controls, planned contrasts, Tukey HSD post-hoc, p<0.05

Table 3

Results on Music Cognition Tasks.

	Controls	AD	FTD	SD
Pitch Discrimination (20)	19.9 (0.2)	19.6 (0.8)	18.5 (2.9)	18.7 (2.2)
Unfamiliar Melody Discrimination (30)	26.1 (2.4)	25.1 (3.2)	24.2 (3.2)	23.7 (5.0)
Familiar Tune Error Detection trials				
Key-violating trials (4)	3.8 (0.5)	3.4 (1.4)	2.7 (1.6)	2.6 (1.6)
Key-preserving trials (4)	3.5 (1.9)	2.7 (1.2)	2.5 (1.5)	2.3 (1.5)
No change trials (4)	3.5 (0.6)	3.5 (0.7)	3.6 (0.9)	3.6 (0.5)

AD = Alzheimer disease, FTD = frontotemporal dementia, SD = semantic dementia

Table 4

Correlation between gray matter regions and music cognition tasks.

Unfamiliar melody discrimination	Anatomical region (BA)	SPM space coordinates (x, y, z)	T value	Z score
right orbito frontal region (11)		25, 59, −19	3.81	3.41
inferior temporal gyrus (20)		29, 6, −50	4.19	3.69
temporal pole (20)		35, 18, −41	3.70	3.33
temporal pole (20)		33, 14, −45	3.63	3.28
left orbito frontal region (11)		−25, 62, −17	4.24	3.72
Familiar melody pitch error detection				
right inferior temporal gyrus (20)		36, 1, −50	4.90	4.17
inferior temporal gyrus (36)		26, 8, −42	4.52	3.91
temporal pole (20)		38, 14, −44	4.21	3.71
superior temporal gyrus (22)		56, −28, 7	3.65	3.29
Familiar melody title recall				
left inferior temporal gyrus (20)		−40, −8, −38	5.75	4.69
temporal pole (38)		−33, 18, −28	5.67	4.64
middle temporal gyrus (20)		−45, −28, −13	5.33	4.44
hippocampus		−25, 2, −29	5.26	4.39
thalamus		−3, 17, 7	4.82	4.12
caudate		−6, 21, 5	4.62	3.99
right inferior frontal gyrus – pars triangularis (48)		37, 22, 14	4.98	4.22
inferior temporal gyrus (20)		42, −1, −44	4.52	3.92
hippocampus		31. −6, −26	3.47	3.16

SPM = statistical parametric mapping, BA = Brodmann area