

Selective impairment of musical emotion recognition in patients with amnesic mild cognitive impairment and mild to moderate Alzheimer disease

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Abstract

Background: Patients with Alzheimer disease (AD) and amnesic mild cognitive impairment (aMCI) have deficits in emotion recognition. However, it has not yet been determined whether patients with AD and aMCI also experience difficulty in recognizing the emotions conveyed by music. This study was conducted to investigate whether musical emotion recognition is impaired or retained in patients with AD and aMCI.

Methods: All patients were recruited from the First Affiliated Hospital of Anhui Medical University between March 1, 2015 and January 31, 2017. Using the musical emotion recognition test, patients with AD ($n = 16$), patients with aMCI ($n = 19$), and healthy controls (HCs, $n = 16$) were required to choose one of four emotional labels (happy, sad, peaceful, and fearful) that matched each musical excerpt. Emotion recognition scores in three groups were compared using one-way analysis of variance (ANOVA) test. We also investigated the relationship between the emotion recognition scores and Mini-Mental State Examination (MMSE) using Pearson's correlation analysis test in patients with AD and aMCI.

Results: Compared to the HC group, both of the patient groups showed deficits in the recognition of fearful musical emotions (HC: 7.88 ± 1.36 ; aMCI: 5.05 ± 2.34 ; AD: 3.69 ± 2.02), with results of a one-way ANOVA confirming a significant main effect of group ($F_{(2,50)} = 18.70$, $P < 0.001$). No significant differences were present among the three groups for the happy ($F_{(2,50)} = 2.57$, $P = 0.09$), peaceful ($F_{(2,50)} = 0.38$, $P = 0.09$), or sad ($F_{(2,50)} = 2.50$, $P = 0.09$) musical emotions. The recognition of fearful musical emotion was positively associated with general cognition, which was evaluated by MMSE in patients with AD and aMCI ($r = 0.578$, $P < 0.001$). The correlations between the MMSE scores and recognition of the remaining emotions were not significant (happy, $r = 0.228$, $P = 0.11$; peaceful, $r = 0.047$, $P = 0.74$; sad, $r = 0.207$, $P = 0.15$).

Conclusion: This study showed that both patients with AD and aMCI had decreased ability to distinguish fearful emotions, which might be correlated with diminished cognitive function.

Keywords: Mild cognitive impairment; Alzheimer disease; Musical emotion; Melody recognition; Brain network

Introduction

The number of studies on the processing of musical emotion in neurodegenerative diseases has increased considerably in recent years. Moreover, in recent decades, a number of studies have investigated musical emotion recognition in the dementia spectrum, including frontotemporal dementia and Alzheimer disease (AD).^[1-6] AD is the most common clinical dementia syndrome. AD has become a major public health problem and has caused an enormous economic burden worldwide.^[7] Amnesic mild

cognitive impairment (aMCI) is a clinical stage on the continuum of cognitive decline between what is considered to be normal aging and dementia. Patients affected with aMCI have a high risk of progressing to AD, with a previous report suggesting an average progression rate of 10% to 15% annually over 5 years.^[8] AD patients not only have cognitive deficits (eg, impaired memory, executive function, and visual perception) but also experience various neuropsychiatric symptoms, such as apathy, depression, aggression, anxiety, and sleep disorders.^[9]

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Music is not only a medium of expression and perceived emotions, but also a reflection of a nation's cultural spirit since the common characteristics of a nation's language (eg, sound sequences with specific rhythmic and melodic patterns) constitute its basic elements.^[10] A meta-analysis showed that music had moderate effects on anxiety and mild effects on behavioral symptoms,^[11] and that it improved the recollection of autobiographical memories in patients with dementia.^[12] Many previous studies have concluded that patients with AD and aMCI have impaired processing of facial emotions, specifically negative emotions (fear, anger, disgust, and sadness), while the recognition of happy emotions were normal.^[6,13-16] However, studies on emotion recognition via auditory channels have reported conflicting results; for example, Testa *et al*^[17] reported that patients with AD had difficulty in recognizing emotions from prosody, whereas Drapeau *et al*^[6] reached an opposite conclusion. Interestingly, studies on patients with localized brain injury have also reported similar results; one study reported that patients who underwent a unilateral temporal lobectomy (including the amygdala) showed no significant differences in processing emotional prosody compared to the control group^[18]; however, Scott *et al*^[19] reported that patients with bilateral amygdala lesions failed to recognize the emotions of fear and anger in voices. Recently, some researchers have begun to pay greater attention to music due to the shortcomings of prosody emotion recognition paradigms; verbal semantics were always associated with the voice tone, while non-verbal aspects of the voice were not exclusively examined.^[6]

Reduced ability to distinguish emotions from surrounding stimuli is a potential factor in impaired social interaction; thus, exploring emotional response to music could help us to better understand the underlying mechanism of dementia. Previous studies have discussed musical emotion recognition in dementia.^[1-6] Most of these studies reported normal processing of musical emotion in patients with AD, with only Hsieh *et al*^[2] reporting impaired processing. A functional neuroimaging study showed that musical emotion recognition was associated with a distributed cerebral network, including the amygdala and its surrounding regions, such as the hippocampus, orbitofrontal and temporal cortices, and anterior cingulate.^[20] Another study reported that some critical cerebral structures (eg, the amygdala and hippocampus) associated with emotional processing were damaged in patients with AD.^[21]

Many studies have concluded that musical emotions are dissociated from musical memory. For example, a well-known patient known as IR who had a damaged bilateral auditory cortex could not distinguish a specific familiar melody, but could accurately distinguish between happy and sad music.^[22] Furthermore, musical memory seems to be preserved in patients with AD,^[23,24] and they can employ mode and tempo to identify musical emotions.^[3,4] Therefore, we speculated that patients with AD would have impaired perception of musical emotions. These previous studies might have failed to conclusively determine whether there is retained ability of emotion recognition in patients with AD either due to only evaluating happy and sad emotions, or insufficient sample sizes.

In the present study, we aimed to investigate whether musical emotion recognition is impaired or retained in patients with AD and aMCI. We also aimed to determine the relationship between the ability to recognize musical emotions and cognitive performance. We hypothesized that recognition of musical emotions would be impaired in patients with AD and aMCI.

Methods

Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University, and all participants provided written informed consent prior to their enrollment in this study.

Subjects

All patients were recruited from the First Affiliated Hospital of Anhui Medical University between March 1, 2015 and January 31, 2017. Using the musical emotion recognition test, patients with AD ($n = 16$), patients with aMCI ($n = 19$), and healthy controls (HCs, $n = 16$) were required to choose one of four emotional labels (happy, sad, peaceful, and fearful) that matched each musical excerpt. All participants underwent standardized assessments of general neuropsychologic functions, and none of them had received formal music training.

Inclusion criteria for patients

The diagnosis of aMCI was discussed in a multidisciplinary staff meeting and was based on the Petersen's criteria,^[25] which require that the general intellectual functioning in patients is preserved, which is confirmed by a score ≥ 24 in the Mini-Mental State Examination (MMSE).^[26] The inclusion criteria for probable AD were consistent with those for the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).^[27] All participants were Chinese native speakers and had a minimum of 6 years of education following primary education. They underwent a neurologic examination including standard magnetic resonance imaging (MRI) scans and an extensive routine neuropsychologic assessment. Patients had to be capable of fully understanding instructions and performing the neuropsychologic assessment. The AD patients' mean score on MMSE was 19.63 ± 3.63 .

Exclusion criteria for all participants

The exclusion criteria were as follows: (1) participants with deficits in hearing or seeing; (2) inability to comprehend task instructions; (3) participants with hyperthyroidism or hypothyroidism, pernicious anemia, and deficiency in vitamin B₁₂ or folate; (4) history of alcoholism or drug dependence and abuse in the participants' lifetime; (5) any significant neurologic disease or any significant systemic illness; and (6) MRI evidence of neoplasm or of the brain demonstrating infection or major focal lesions.

Musical emotion recognition test

We used 40 instrumental musical excerpts from the classic Western tonal system intended to induce happiness, peacefulness, sadness, and fear (10 musical examples for each target emotion). The stimuli were computer generated and were presented in a random order with each excerpt lasting approximately 15 s. The music tracks were played again if requested. In a forced-choice paradigm, the participants were required to select one of four emotion labels (happy, peaceful, sad, or fearful) to match each musical excerpt. The primary index of our study was defined as the accuracy of identifying each emotion type.

Statistical analysis

Statistical analyses were performed with SPSS software, version 17 (SPSS Inc., Chicago, IL, USA). Data were represented as the mean ± standard deviation (SD) or median (Q1, Q3). Comparisons based on gender variables among patients with AD and aMCI and the HC were performed using Chi-squared test. Variables were checked for normality of distribution using the Kolmogorov-Smirnov test. Parametric data were compared among the three groups using one-way analysis of variance (ANOVA). Comparisons were performed using Kruskal-Wallis test for non-parametric data. Follow-up multivariate analysis of variance (MANOVA) was conducted to further delineate the group differences in each emotion, followed by post-hoc analysis to examine specific group differences. The Kruskal-Wallis test was used to compare non-parametric data in individual groups; post-hoc group comparisons were performed using the Mann-Whitney U test. Pearson’s correlation analysis was conducted to examine the possible relationship between the MMSE score and the recognition of musical emotions. The level of statistical significance was defined as $P < 0.05$.

Results

Demographic and neuropsychologic characteristics of subjects

Finally, this study included 16 patients with AD (10 men and 6 women, mean age: 70.7 ± 11.6 years), 19 patients

with aMCI (9 men and 10 women, mean age: 69.5 ± 8.9 years), and 16 HC (5 men and 11 women, mean age: 68.7 ± 8.2 years). The demographic and neuropsychologic characteristics of all participants are shown in Table 1. The three groups were well matched for age, gender, and educational level. The ANOVA results indicated that there were significant differences among the three groups in all of the investigated behavioral data (all $P < 0.001$) except for the digital span forward ($F_{(2,50)}=2.137, P = 0.129$). Post-hoc comparisons revealed that the behavioral performance in the digital span backward was comparable between the aMCI group and the HCs ($U = 121.50, Z = -1.06, P = 0.320$), and between the aMCI and the AD groups ($U = 83.00, Z = -2.38, P = 0.220$). In addition, there were no significant differences in the auditory verbal learning test scores between the aMCI and AD groups (delayed recall: $U = 81.00, Z = -2.54, P = 0.180$; delayed recognition: $U = 94.50, Z = -2.38, P = 0.560$); however, all other test scores showed significant group differences (all $P < 0.001$). In particular, the MMSE score dropped significantly from the HC to the patients with aMCI and from the patients with aMCI to the patients with AD.

Recognition of musical emotion

For the accuracy of the recognition of musical emotion, a one-way ANOVA revealed a significant main effect of group (fearful, $F_{(2,50)}=18.703, P < 0.001$, Table 2). To determine differences between individual groups, a Student-Newman-Keuls (SNK) test was also used for analyses. Post-hoc analysis suggested that patients with AD and aMCI showed deficits in the recognition of fearful musical emotions compared to HC (SNK, $P < 0.050$ for both), and that there was no significant difference between the patients with AD and aMCI in the recognition of fearful musical emotions (SNK, $P > 0.050$). No significant differences were present among the three groups for the happy ($F_{(2,50)}=2.572, P = 0.087$), sad ($F_{(2,50)}=2.495, P = 0.093$), or peaceful ($F_{(2,50)}=0.383, P = 0.684$) musical emotions by using a one-way ANOVA test.

To further delineate the group differences within each emotion category, the scores for recognition of the four

Table 1: Demographic and neuropsychologic characteristics of all participants in this study.

Characteristics	HC (n = 16)	aMCI patients (n = 19)	AD patients (n = 16)	Statistical values	P
Male/female	5/11	9/10	10/6	3.317*	0.210
Age (years)	68.7 ± 8.2	69.5 ± 8.9	70.7 ± 11.6	0.174†	0.841
Education duration (years)	11.2 ± 3.7	10.8 ± 3.6	10.8 ± 4.5	0.062†	0.940
MMSE score	28.63 ± 1.20	25.16 ± 2.91	19.63 ± 3.63	42.624‡	<0.001
VFT	18.13 ± 3.26	13.95 ± 3.88	10.44 ± 3.18	19.530‡	<0.001
DS (f)	6.94 ± 1.18	6.26 ± 1.32	6.00 ± 1.46	2.137†	0.129
DS (b)	4.19 ± 0.75	3.74 ± 1.15	2.88 ± 0.62	9.053‡	<0.001
AVLT (immediate recall)	8.00 (7.00, 9.00)	3.00 (1.00, 5.00)	1.50 (0, 2.75)	30.351‡	<0.001
AVLT (delayed recall)	8.00 (7.00, 9.00)	4.00 (0.00, 6.00)	0.00 (0, 1.50)	32.441‡	<0.001
AVLT (delayed recognition)	14.00 (13.25, 15.00)	12.00 (11.00, 14.00)	10.50 (5.50, 12.00)	11.800‡	<0.001

The data are shown as n, mean ± standard deviation, or median (Q1, Q3). * Chi-squared test. † One-way analysis of variance test. ‡ Kruskal-Wallis test. HC: Healthy control; aMCI: Amnesic mild cognitive impairment; AD: Alzheimer disease; MMSE: Mini-Mental State Examination; VFT: Verbal fluency task; DS (f): Digital span (forward); DS (b): Digital span (backward); AVLT: Auditory verbal learning test.

Table 2: Emotion recognition scores in HC, aMCI, and AD groups.

Emotion recognition scores	HC (n = 16)	aMCI patients (n = 19)	AD patients (n = 16)	Statistical values*	P
Happy	9.50 ± 0.63	9.00 ± 0.82	8.94 ± 0.85	2.572	0.087
Peaceful	7.25 ± 1.95	6.63 ± 2.16	6.94 ± 2.11	0.383	0.684
Sad	8.06 ± 2.32	6.84 ± 2.65	5.94 ± 3.09	2.495	0.093
Fearful	7.88 ± 1.36	5.05 ± 2.34	3.69 ± 2.02	18.703	<0.001

The data are shown as mean ± standard deviation. * One-way analysis of variance test. HC: Healthy control; aMCI: Amnesic mild cognitive impairment; AD: Alzheimer disease.

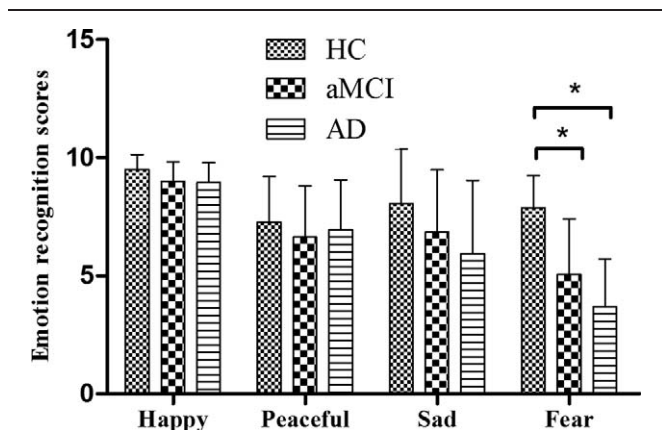


Figure 1: Recognition of musical emotions in the HC, aMCI, and AD groups. These analyses were performed using a one-way analysis of variance test. * $P < 0.001$. AD: Alzheimer disease; aMCI: Amnesic mild cognitive impairment; HC: Healthy control.

emotions were analyzed using a MANOVA. Results showed a significant overall group difference (Hotelling’s trace; $F_{(9,90)} = 2.857, P < 0.001, \eta^2 = 0.321$), as well as significant group differences in the recognition of fearful ($F_{(2,48)} = 18.703, P < 0.001, \eta^2 = 0.438$) [Figure 1]. However, we found no significant group differences in the recognition of the other emotions (happy: $F_{(2,48)} = 2.572, P = 0.087, \eta^2 = 0.097$; peaceful: $F_{(2,48)} = 0.383, P = 0.684, \eta^2 = 0.016$; sad: $F_{(2,48)} = 2.495, P = 0.093, \eta^2 = 0.94$) using a MANOVA test.

Correlation between musical emotion recognition and neurocognitive test performance

We examined the relationship between the recognition of emotion and the MMSE score. It demonstrated a significant correlation between the MMSE scores and recognition of fearful emotions ($r = 0.578, P < 0.001$) in patients with AD and aMCI [Figure 2]. The correlations between the MMSE scores and recognition of the remaining emotions were not significant (happy: $r = 0.228, P = 0.110$; peaceful: $r = 0.047, P = 0.740$; sad: $r = 0.207, P = 0.150$). However, we found a significant correlation between correct recognition of fearful emotions and the performance in the other cognitive tests (verbal fluency test: $r = 0.360, P = 0.010$; auditory verbal learning test: immediate recall, $r = 0.572, P < 0.001$; delayed recall, $r = 0.623, P < 0.001$; and delayed recognition, $r = 0.458, P < 0.001$). No correlations were found between the digital span forward or backward and recognition of any of the emotions, except for digital span backward and recognition

of fearful emotion (digital span forward: happy, $r = 0.060, P = 0.676$; peaceful, $r = 0.026, P = 0.859$; sad, $r = -0.052, P = 0.717$; fearful, $r = 0.170, P = 0.234$; digital span backward: happy, $r = 0.141, P = 0.325$; peaceful, $r = 0.014, P = 0.924$; sad, $r = 0.125, P = 0.380$; fearful, $r = 0.501, P < 0.001$).

Discussion

The main finding of this study showed that musical emotion recognition was relatively affected in patients with aMCI and AD compared to the HC. Patients with AD and aMCI performed worse in the recognition of fearful musical emotions compared to the HC, while the recognition of the other three musical emotions (happy, peaceful, and sad) was unaffected. The ability to recognize fearful musical emotions was positively correlated with traditional general cognition.

To our knowledge, this was an important study that has adopted the musical emotion recognition test to examine musical emotion recognition in patients with AD and aMCI. The finding that recognition of fearful musical emotion was impaired in patients with AD and aMCI was consistent with those of previous behavioral studies that showed deficits in recognition of fearful emotions in different tasks among these patients. Based on previous findings on recognition of facial expressions in patients with AD and aMCI, we believed that the ability to recognize fearful emotions in these patients was impaired regardless of whether the stimulus is visual or auditory.^[13-15] Indeed, some studies have found that voice or prosody distinction was impaired in patients with AD.^[17,28] Moreover, other studies have reported that the ability to apply two musical structural determinants (mode and tempo) to distinguish happy and sad emotions differed with age.^[3,4] For example, Matthews *et al*^[29] reported a case of a young man with auditory agnosia as a consequence of cortical neurodegeneration who still retained pleasurable emotional responses to music. To exclude the possibility that the impairment in recognition of fearful emotion was due to fearful music being more difficult to distinguish than other emotions, we compared the recognition of the four musical emotions in the HC group. No significant differences were found in the recognition of fearful emotion compared to the sad and peaceful emotions.

Our results revealed that impaired emotion recognition might not be specific to arousal or valence, but instead showed that variations might be specific to specific

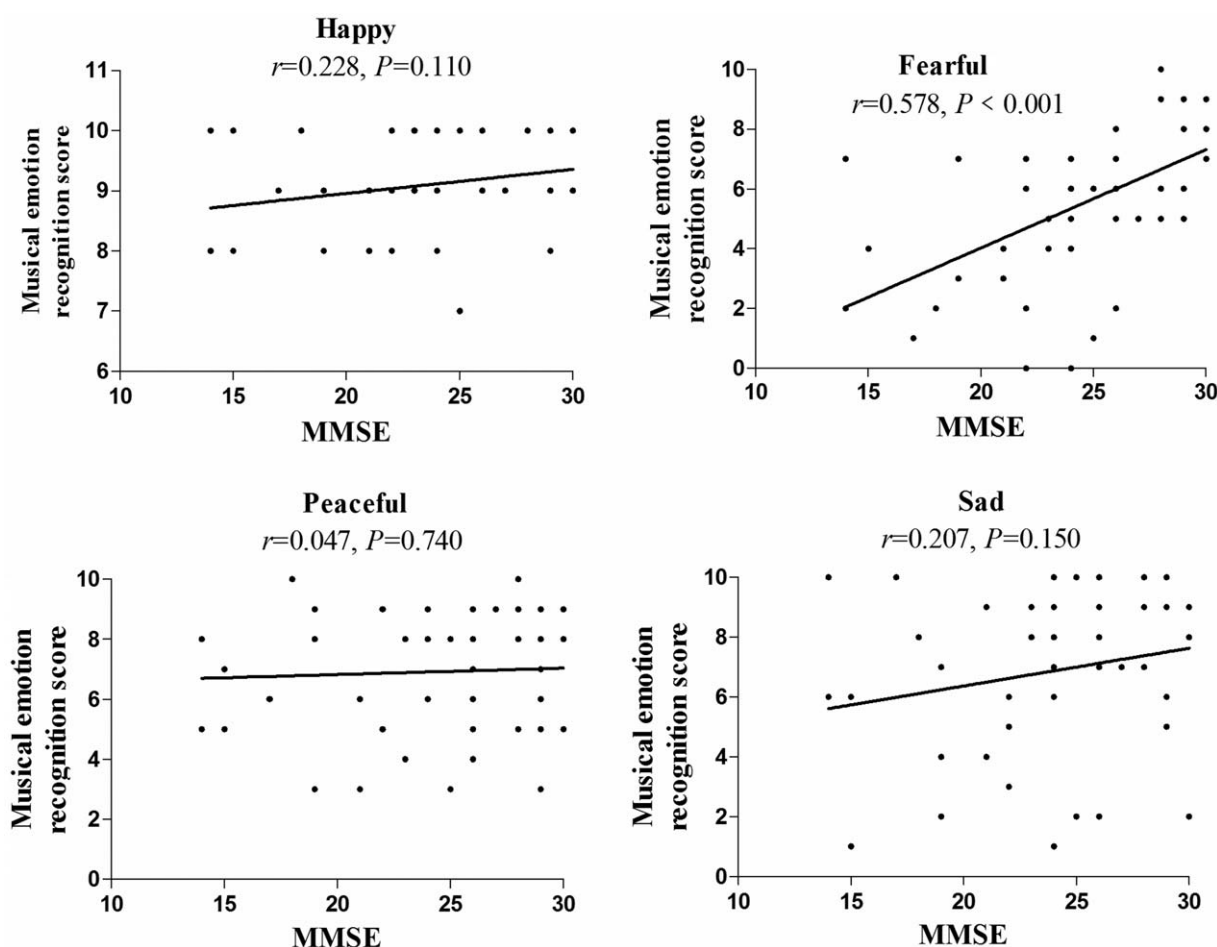


Figure 2: Correlation between MMSE scores and four types (happy, fearful, peaceful, and sad) of music recognition performance. These analyses were performed using Pearson's correlation analysis test. MMSE: Mini-Mental State Examination.

emotions, which was in agreement with the results of previous studies on facial and vocal emotion recognition during the adult life span.^[30,31] Focal cerebral lesions have demonstrated that the amygdala was a key structure for processing fearful emotions. For example, Gosselin *et al*^[32] investigated emotion recognition in patients with unilateral anteromedial temporal lobe resection (including the amygdala) for the relief of medically intractable epilepsy, and found that the subjects were unable to identify fearful emotions from facial expressions and musical stimuli, suggesting that the amygdala could be a multimodal structure. Calder *et al*^[30] showed that an increase in age produced a progressive reduction in the recognition of fear that began at approximately 40 years of age, whereas recognition of happy emotions was not affected by age. This suggested that certain emotions could be mainly regulated by a relatively specific neural region, which was indeed the case. Borg *et al*^[33] reported a case of a patient who showed a selective deficit in recognizing facial expressions of disgust following damage to the left posterior insular cortices. Another meta-analysis of emotional activation using positron-emission tomography and functional MRI (fMRI) found that the amygdala was particularly associated with fear, whereas the basal ganglia/ventral striatum regions were associated with

happiness.^[34] The prominent feature of AD on the MRI scans was atrophy of the hippocampus and entorhinal cortex. However, recent studies have reported that the amygdala showed significant gray matter volume loss on double inversion recovery images in the AD group,^[35] while Xu *et al*^[36] found changes in the amygdala volume in different stages of aMCI. Taking all of these findings into account, it was not surprising that the patients with AD and aMCI in our study failed to recognize the fearful musical emotion but could identify happy emotion. The decrease in performance of emotion recognition from the aMCI to the AD group might be due to damaged structure or function of the amygdala, which was in agreement with a previous study that showed increased progression in low-intensity facial emotion recognition deficits from the HC to patients with aMCI to patients with mild AD.^[13]

In the current study, we did not perform functional neuroimaging examination; therefore, we could not directly correlate the selective impairment of musical emotion recognition with the degeneration of any neural structures. However, neuroimaging and lesion studies have provided abundant evidence of hemispheric asymmetries in the processing of emotional expressions. For instance, Khalifa *et al*^[37] showed that epileptic patients with right or

left anterior mesiotemporal resection (including the amygdala) had impaired recognition of sad musical emotion, whereas recognition of happy musical emotion was only reduced by left resection. Another study suggested that both left and right temporal resections impaired the recognition of fearful music,^[38] which seemed to indicate that the left temporal lobe was associated with processing of both negative and pleasant emotions. Previous functional neuroimaging studies also suggested that the left amygdala was most closely linked to happiness.^[39] Moreover, some studies, regardless of the modality used (visual or auditory stimulation), have demonstrated that impairment of comprehension of emotions with negative valence was predominantly correlated with atrophy in the right amygdala, right orbital frontal cortex, and temporal pole,^[2,40] with a meta-analysis also sharing the same conclusion.^[41] Based on our results and those of the previously mentioned studies, we speculated that the progression of AD damaged the right cerebral hemisphere which processed emotion signals; thus, the need for a more accurate methodology to determine subtle differences is urgent. Overall, these studies showed that several cortical and sub-cortical structures involved in musical emotion recognition may be affected early on by neurodegeneration in aMCI and AD.

However, it is evident that other plausible interpretations might exist. First, music is universal across all human societies. Feelings of pleasure while listening to music are due to activated reward pathways in our brains and automatic endogenous dopamine release in the striatum, which can reinforce biologically adaptive behaviors such as eating, as well as behaviors related to love and sex.^[42] Therefore, patients with dementia may preserve memories of pleasure because of their positive state, and to some extent suppress fearful emotions due to the uncomfortable feelings aroused; thus, fearful emotions might be more difficult to identify than happy emotions. Second, it is worth noting that scary stimuli are more variable in structure, contain varying degrees of dissonance and irregularity, and lack specific structural features that can help participants to distinguish them from others.^[38] Lastly, our correlation analysis seemed to suggest that a relatively intact cognitive function was more crucial to processing fearful rather than happy music.

In summary, the results of the current study supported the existence of selective impairment of recognition of fearful musical emotion in patients with aMCI and AD, rather than a global difference in recognition of the four types of musical emotions. Disease-related deterioration of the amygdala may explain the disease-related difference in the recognition of fearful musical emotion that was observed in patients with aMCI and AD. Additional experiments manipulating potentially key variables are required. Further studies combining the musical emotion recognition test with fMRI are required to further explore the disease-related differences in recognition of different musical emotion, and to determine the neural basis of the role played by the amygdala in emotion recognition.

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Conflicts of interest

None.

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