Title page:

The Effects of Music Therapy on Cognition, Psychiatric Symptoms and Activities of Daily Living in Patients with Alzheimer's Disease

Running title:

Efficacy of Music therapy for AD

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Abstract

Backgrounds: Alzheimer's disease (AD) is the most common type of dementia, affecting millions of older people worldwide. However, pharmacological therapies have not resulted in desirable clinical efficacy in the past decades. Non-pharmacological therapies have been receiving increased attention to treat dementia in recent years.

Objectives: This study explores the effects of music therapy on cognitive function and mental wellbeing of patients with AD.

Methods: A total number of two hundred and ninety-eight AD patients with mild, moderate, or severe dementia participated in the study. The participants with each grade of severity were randomly divided into three groups, which were a singing group, a lyric reading group and a control group. These three groups received different interventions for three months. All participants underwent a series of cognitive, neuropsychological and activities of daily living tests at baseline, three months and six months later.

Results: In general, our analysis shows that music therapy is more effective for improving verbal fluency and for alleviating the psychiatric symptoms and caregiver distress than lyrics reading in patients with AD. Stratified analysis shows that music therapy is effective for enhancing memory and language ability in patients with mild AD, reducing the psychiatric symptoms and caregiver distress in patients with moderate or severe AD. However, no significant effect was found for activities of daily living in patients with mild, moderate or severe AD.

Conclusions: This study suggests that music therapy is effective in enhancing cognitive function and mental wellbeing and can be recommended as an alternative approach to manage AD associated symptoms.

Key words: Music therapy; Dementia; Memory; Language;

INTRODUCTION

Alzheimer's disease (AD) is a progressive and fatal brain degenerative disease [1]. AD is the most common type of dementia in older people, and accounts for 60% of the dementia [2, 3]. This cerebral manifestation causes gradual memory loss and decline in cognitive function, which progressively affects the activities of daily living (ADL). Patients with AD commonly experience neuropsychiatric and behavioral symptoms, which causes substantial distress for AD patients and their caregivers [4]. Dementia brings a considerable burden to families and is becoming a major challenge for many countries [5]. However, pharmacological therapies have not resulted in desirable clinical efficacy, and non-pharmacological therapies have been receiving increased attention as an alternative first-line approach for demented people. A broad array of such interventions has been developed over the past two decades, such as cognitive training [6] , sensory stimulation [7], music therapy [8] , and motor stimulation [9].

Music therapy is the application of music and/or its elements (melody, rhythm, harmony, and sound) by qualified musical therapists. Participants can passively listen to music or actively participate in singing and playing an instrument. Music has been used in the management of dementia associated symptoms for many years [10, 11]. Parbery-Clark reported that elderly musicians showed greater auditory working memory compared to non-musicians, and suggested that musical training may help mitigate the impact of age-related cognition declines [12]. By listening to music, patients with AD showed improvement in categorical word fluency [13], autobiographical memory [14], and the memory of the lyrics [15]. Furthermore, music has been found to facilitate performance during various kinds of cognitive (including non-linguistic) tasks [16]. Results from these studies suggest that music therapy could be effective for maintaining cognitive function in the elderly with or without dementia. Musical interventions have also been used to improve social skills, emotional and neuromotor function

[17], and to manage behavioral and psychological symptoms of dementia (BPSD) [11, 18].

Though the mechanism of music therapy for AD is not fully known, there are some evidence and theories to explain its effects. Some studies show that various parts of the brain are involved in the music therapy, including subcortical structures such as basal ganglia, nucleus accumbens, ventral tegmental area, hypothalamus, and cerebellum [19-21] and cortical structures such as medial prefrontal cortex [22] and orbitofrontal cortex [23]. As these areas are less affected than medial temporal lobe in AD, music therapy could enhance memory function more effectively than speech therapy. Besides, dual coding of lyrics and melody may lead to a stronger memory trace, which enhances long-term retention. Satoh, et al (2015) conducted a study of singing therapy on patients with AD using the functional magnetic resonance imaging (fMRI) scans. The study suggested that singing possibly improves cognitive function through organizing a new cognitive strategy [24]. The fMRI analysis shows signs of new cognitive activities in the right angular gyrus of the anterolateral region and the left lingual gyrus of the occipital lobe during the study period, which suggests that singing stimulates the language centre and the logic processing area of the brain [24]. Moreover, another study found that singing songs is more effective than reading lyrics, which suggests that the brain region for processing music could be redundant in patients with AD but singing might stimulate this redundant area allowing reconnection and improving memory [25]. The strong connection between singing and speaking suggests that the singing component of music therapy enhances linguistic ability and memorization [26].

However, some scholars argue the effectiveness of music therapy on dementia. A recent review reported that music-based therapeutic interventions may have little or no effect on the emotional well-being or quality of life, overall behavioral problems and cognition [27]. Thus further research with larger sample size needs to be carried out and the relation between the

benefits and duration of music therapy should be considered. Therefore this randomized controlled trial was conducted to explore the effects of music therapy on cognition, BPSD, and ADL of AD patients and their caregiver distress. In order to provide robust evidence of music therapy, we followed the participants up for three months to observe how its effects would last after completion of the music intervention. In order to further examine if the severity of dementia influence the efficacy in different ways, we enrolled AD patients with mild, moderate, or severe dementia and the participants with each grade of severity were divided into three groups (the singing group, the lyric reading group, and the blank control group) randomly.

MATERIALS AND METHODS

Participants and procedure

This study was conducted from Aug 2014 to Dec 2016 in the Center for Cognitive Disorders of Beijing Geriatric Hospital, China (Trial registration number: ChiCTR-TRC-14005031, http://www.chictr.org.cn). The inclusion criteria were as follows: (a) 65 years old and older, (b) with diagnosis of probable AD based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Participants were excluded if they were experiencing any of the following conditions: (a) hearing difficulty even with wearing hearing aids, (b) obvious difficulty in communication, (c) any other conditions which may disturb assessments or interventions. Two hundred and ninety eight participants were recruited and were assessed with the Clinical Dementia Rating scale (CDR)[28] , which is a rating scale for the clinician to characterize the degree of severity of dementia (0 = no dementia, 0.5 or 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia). Ninety six of the AD participants were with mild dementia (mild AD), 100 with moderate dementia (moderate AD)

and 95 with severe dementia (severe AD). The participants with each grade of severity were then allocated into three groups randomly (Figure 1).

Enrollment Randomization and allocation

Participants were enrolled by dementia specialists in the research team. A non-medical research assistant (RA) carried out the randomization, but was not involved in the enrollment, assessment, or intervention of the participants. The RA generated random number sequence using SAS software for the participants with different severity levels of dementia respectively. Then the RA produced sealed envelopes with the serial number outside and group number inside and kept the envelopes in a locked drawer which was inaccessible to all the researchers. The envelopes were opened sequentially by the RA after baseline assessments and assigned participants with different severity levels of dementia to the three groups equally according to the group number printed inside the envelopes. Outcome evaluators and data analysts were blinded to the group assignment.

Table 1 illustrates that the Group A is the singing group（defined as music therapy group）(total n=100, mild AD n=33, moderate AD n=34, severe AD n=33), Group B is the lyric reading group (total n=99, mild AD n=31, moderate AD n=34, severe AD n=34), and Group C is the blank control group (total n=99, mild AD n=32, moderate AD n=35, severe AD n=32). None of the participants had professional music experience before.

The study was approved by the scientific and ethical committees of the Beijing Geriatric Hospital, Beijing, China. Informed consents were obtained from all participants or their guardians.

Interventions

Group A received music therapy by singing or listening to their familiar and favorite songs, in which they especially loved in their twenties and thirties. Most of the songs are classic and soothing. Group B read the lyrics without the melody of their familiar and favorite songs, and they also loved these songs in their twenties and thirties. Both the music therapy and the lyric reading therapeutic exercise were practiced in groups with one therapist to five to six participants and were carried out twice daily, with one session in the morning and one session in the afternoon for 3 months, which lasted 30-40 minutes per session. A three-month follow up assessment was carried out after the completion of the intervention. Group C as a control group received no special interventions. All three groups received routine medical treatment during the study period. This medical treatment included taking conventional medicines combining with other daily care and support.

assessments

All participants were assessed with the following measurements three times at three months intervals. The first assessment referred as t_0 took place prior to the commencement of the different group intervention, the second assessment as t_1 (at 3 months after the commencement of different group intervention), and the third assessment as t_2 (at 6 months after the commencement of different group intervention). The timeline of assessments and measures are described in Fig. 1.

Cognitive Function Assessment

The Cognitive Function Assessment contains the mini mental state examination (MMSE), the World Health Organization University of California-Los Angeles, Auditory Verbal Learning Test (WHO-UCLA AVLT) and the semantic verbal fluency test.

The MMSE[29] was used to assess the participants' overall cognitive function. It includes multiple domains of cognitive function, comprising of orientation, registration, attention and calculation, recall, language and praxis. The maximum achievable score is 30.

The WHO-UCLA AVLT[30] was used to evaluate the participants' short-term and long-term memory by scoring their performance on immediate recall and delayed recall respectively. After learning 15 verbal words, the subjects were required to repeat the words immediately and 30 minutes later.

Language function was assessed with semantic verbal fluency test. It required the participants to speak out as many words as possible within 60 seconds from a given category, such as animals or vegetables. One-minute animal verbal fluency task was used in this study.

Neuropsychiatric and Behavioral Symptom Assessment

The Neuropsychiatric Inventory (NPI) [31] were used to assess neuropsychiatric symptoms in AD patients and related caregiver distress. It examines 10 factors of behavioral problems. These factors comprise delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor activity. Each factor is evaluated in terms of severity (0-3 points) and symptom frequency (0-4 points). The scoring index includes factor scores (frequency × severity) and a total score (0–120 points). Higher scores represent more severe psychiatric symptoms. The degree of distress on caregivers caused by each factor was also assessed and then the sum score was compiled.

ADL Assessment

The Barthel Index[32] is an ordinal scale that measures performance on ADL. It uses ten variables describing ADL and mobility, including fecal incontinence, urinary incontinence,

help needed with grooming, toileting, feeding, transferring, walking, dressing, climbing stairs and bathing. Each item is rated with a given number of points assigned to each level or rank. Higher scores on the Barthel Index indicate greater independence (total score ranges from 0 to 100).

All data for this study were collected by a specially trained medical team of doctors, nurses and medical students. A test was performed to all investigators after training and the internal consistency coefficient on the evaluation and data collection was above 0.90.

Primary and secondary outcomes

The psychometric tools used in this study were analyzed to assess the efficacy of the music therapy. The primary study aim was to evaluate the extent to which music therapy impacted the language function of AD patients (measured by verbal fluency test score), so the verbal fluency test score was selected as the primary outcome. Secondarily, we aimed to evaluate changes in NPI score, which measures BPSD. Results of other assessments were also analyzed.

Statistical Analyses

One-way ANOVA is used to test the difference in the mean values of continuous data between three groups. If the test result of ANOVA was significant, a multiple comparison was conducted using Fisher's Least-Significant Difference (LSD) to test the exact group difference. The mean difference of two groups is denoted by Δ. The Pearson Chi-square test was used to analyze all the categorical data from groups. Data were analyzed using IBM SPSS Statistics 20.0 . A value of $p < 0.05$ was considered statistically significant.

RESULTS

During the study period, only 10 out of the 298 participants dropped out from the study, in which three participants left the study due to changing residence and seven left due to the occurrence of new medical problems (including 4 patients with pneumonia, 3 patients with bone fracture). They are three participants from Group A (1 with mild AD, 2 with severe AD), three from Group B (1 with mild AD, 2 with severe AD), and four from Group C (1 with mild AD, 3 with severe AD). This resulted in a remaining sample of 97 participants in Group A and of which 89 participants were able to sing the songs during the whole of the study period and 8 participants with severe dementia were unable to follow the pace of the therapy at some times, 96 participants in Group B, and 95 participants in Group C, which maintained relatively balanced sample sizes for comparison groups that were set originally for this study (Table 1). The data analysis includes a sample of 288 AD patients.

The first part of Table 2 presents the descriptive statistics of demographic characteristics and medical treatment. There was no significant difference of age, gender, education level and medical treatment received during the study period between three groups (P>0.05).

Analyzing test scores of all participants

First, we analyzed test scores of 288 patients with AD who completed this study (Group A, n=97; Group B, n=96; Group C, n=95). The second part of Table 2 shows the results of outcome variables measured by the MMSE, WHO-UCLA AVLT (including immediate recall and delayed recall), verbal fluency test, NPI, and Barthel Index at t_0, t_1 and t_2.

The results of MMSE, WHO-UCLA AVLT, Barthel Index show there is no significant difference found in all three assessments of the three groups.

Verbal Fluency Test

In verbal fluency test, there were significant differences among three groups at t_1 (5.85±1.04, 5.92±1.54, 5.48±1.86, F=16.35, P<0.05) and t_2 (5.78±1.09, 5.68±1.37, 5.41±1.51, F=14.81, P<0.05). Both Group A (Δ=0.37, P<0.05) and Group B (Δ=0.44, P<0.05) scored higher than Group C, and there were no statistically significant difference between Group A and Group B at t_1. Only Group A scored higher than Group C (Δ=0.37, P<0.05), but there were no significant difference between Group B and Group C at t_2.

NPI

In NPI, there were significant differences among three groups at t_1 (20.00±12.63, 21.85±11.34, 24.99±12.35, F=15.66, P<0.05) and t_2 (19.36±12.24, 22.08±12.01, 25.22±11.38, F=13.94, P<0.05). Both Group A (Δ=－4.99, P<0.05) and Group B (Δ=－3.14, P<0.05) scored lower than Group C, and there were no statistically significant difference between Group A and Group B at t_1. Group A scored lower than both Group B (Δ=－2.72, P<0.05) and Group C (Δ=－5.86, P<0.05), but there were no statistically significant difference between Group B and Group C at t_2.

Analyzing test scores of participants with mild AD

We analyzed test scores of 93 patients with mild AD who completed this study (Group A, n=32; Group B, n=31; Group C, n=30). Table 3 shows the results of outcome variables as mentioned above.

The results of MMSE, NPI and Barthel Index show there is no significant difference found in all three assessments of the three groups.

WHO-UCLA AVLT

There were significant differences among three groups in the WHO-UCLA AVLT immediate recall (7.38±1.45, 6.93±1.34, 6.63±1.26, F=17.42, P<0.05) and delayed recall (6.51±1.52, 5.88±1.26, 5.57±1.10, F=20.49, P<0.05) at t_1. Group A scored higher than Group B and Group C in both immediate recall (Δ=0.45, P<0.05; Δ=0.75, P<0.05) and delayed recall (Δ=0.63, P<0.05; Δ=0.94, P<0.05) at t_1. There were no significant statistical difference between Group B and Group C in both immediate recall test and delayed recall test at t_1. There were no significant difference among three groups in the WHO-UCLA AVLT immediate recall or delayed recall at t_2.

Verbal Fluency Test

There were significant differences among three groups in the verbal fluency test scores at t_1 (8.63±1.94, 8.58±1.75, 7.54±2.03, F=17.56, P<0.05) and t_2 (8.45±1.69, 7.89±1.74, 7.43±1.52, F=14.37, P<0.05). Both Group A (Δ=1.09, P<0.05) and Group B (Δ=1.04, P<0.05) scored higher than Group C and there were no significant statistical difference between Group A and Group B at t_1; Group A scored higher than Group B (Δ=0.56, P<0.05) and Group C (Δ=1.02, P<0.05) and there were no significant statistical difference between Group B and Group C at t_2.

Analyzing test scores of participants with moderate AD

One hundred participants with moderate AD completed this study (Group A, n=34; Group B, n=33; Group C, n=33). Table 4 shows the results of outcome variables as mentioned above.

The results of MMSE, WHO-UCLA AVLT, verbal fluency test, Barthel Index show there is no significant difference found in all three assessments of the three groups.

NPI

Though there was a trend that Group A scored lower than Group B and Group C at t_1 and t_2, the difference is not statistically significant in NPI score. However, in NPI caregiver distress scale, there were significant differences among three groups at t_1 (20.73±10.16, 28.90±12.90, 30.55±19.13, F=18.31, P<0.05) and t_2 (21.00±13.63, 29.54±14.86, 31.10±13.14, F=19.88, P<0.05). Group A scored lower than Group B (Δ=－8.17, P<0.05; Δ=－8.54, P<0.05) and Group C (Δ=－9.82, P<0.05; Δ=－10.1, P<0.05) at t_1 and t_2.

Analyzing test scores of participants with severe AD

Ninety-five participants with severe AD completed this study (Group A, n=31; Group B, n=32; Group C, n=32). Table 5 shows the results of outcome variables.

The results of MMSE, WHO-UCLA AVLT, Verbal Fluency Test, Barthel Index show there is no significant difference in all three assessments of the three groups.

NPI

In NPI, there were statistically significant differences among three groups at t_1 (26.57±10.35, 31.27±15.36, 35.35±16.45, F=16.51, P<0.05) and t_2. (25.96±14.23, 32.43±15.31, 35.43±14.36, F=16.23, P<0.05). Group A scored lower than Group B (Δ=－4.7, P<0.05; Δ=－6.47, P<0.05;) and Group C (Δ=－8.78, P<0.05; Δ=－9.47, P<0.05) at both t_1 and t_2. Moreover, in caregiver distress scale, there were statistically significant differences among three groups at t_1 (25.12±13.30, 35.64±17.04, 39.57±16.34, F=17.29, P<0.05) and t_2 (25.02±13.47, 36.78±13.47, 40.38±17.31, F=18.13, P<0.05). Group A scored lower than Group B (Δ=－10.52, P<0.05; Δ=－11.76, P<0.05) and Group C (Δ=－14.45, P<0.05; Δ=－15.36, P<0.05) at both t_1 and t_2.

DISCUSSION

AD is a neurodegenerative disease characterized by cognitive decline, which progressively affects the ability of self-maintaining ADL. Impairment in memory is the most common and predominant cognitive deficit in AD, but deficits in other cognitive domains (language, executive function, and visuospatial skills) are also present. People with AD often experience some behavioral disturbances. Up until now there is no effective pharmacological treatment that can control the progress of AD disease. Music therapy stimulates various aspects of cognitive function and supports emotional, social and physical needs, such as enhancing expression of one's feelings, communication, learning and building new relationships. Singing, combines language, music and instinctive human behavior that can enhance neurological stimulation[8]. These links produce a positive effect on all of those involved in the care or management of dementia and people with dementia[33].

This study shows that music therapy has positive effect on the ability of immediate and delayed word recall in mild AD patients. This result can be explained by the hypothesis that singing arouses the region in charge of music processing in the brain may be less utilised in patients with AD, which helps improve memory and attention. [34]. However, this effect did not sustain longer than 3 months after the intervention completed. This result indicates that continuous music therapy could be beneficial to people with AD in a long run or in a longer term.

In a clinical setting, short (i.e., music played as a background in a memory task) and long-lasting (i.e., in a music-therapy program) auditory stimulations with music were shown to improve both category fluency in a verbal fluency task in older people with or without AD[13], and speech content as well as fluency in patients with dementia[35]. In this study, the verbal fluency test score of patients with mild AD were higher in the music therapy group

than the other two groups after 3 months of intervention and this effect sustained till 3 months after the intervention completed. This result shows evidence that music therapy may activate a wider range of neural networks with the stimulation of musical melodies, thus enabling language functions to be largely maintained and brought into play. Therefore, music therapy could be used as speech and language training for people with AD.

In this study the music therapy was found to be effective on controlling psychiatric and behavioral symptoms in patients with severe AD. Its results show that music therapy reduced the psychiatric symptoms as well as the caregiver distress for patients with advanced dementia, This result is consistent with previous studies; Guetins's study has confirmed that music has a therapeutic effect on anxiety and depression in patients with mild to moderate dementia[36], and a Japanese study found that music therapy effectively improved emotional and psychiatric symptoms in severe AD patients[37]. Group music interventions may help improve social interaction between people with dementia, promoting relaxation and reducing levels of agitation[38].

In conclusion, this randomly controlled trial with 288 participants of AD patients explored the effects of music on memory, language and psychiatric conditions and activities of daily living in patients with different severities of AD. We found that music therapy can enhance memory and language ability in patients with mild AD, and can reduce the psychiatric symptoms of the patients with advanced AD as well as the level of the distress encountered by their caregivers. The training sessions of singing songs are more effective than reading lyrics of the songs, which add further evidence to the effectiveness of music therapy for treating patients with AD.

There are some limitations of this study. We did not take the participants' familiarity with music into consideration in study design, and their ability to sing was not assessed for this

research. However none of the participants received professional training in music or singing in the past, thus the bias is minimized. Moreover, it showed that even though they were not singers, they could all cooperate with singing, listening or reading during the study.

Acknowledgments

The authors thank all participants and their families for their involvement and cooperation. This study was funded in China by the Beijing Municipal Science & Technology commission (Z151100004015023) and Major Clinical Medicine Development Plan of Beijing Municipal Administration of Hospitals (Project number ZYXL201834).

Conflict of Interest

None declared.

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Table 1. Composition of the groups

number	Music therapy group (Group A)	Lyrics controlled therapy group (Group B)	Control group (Group C)	total
Mild AD	33 (1*)	31	32 (2*)	96(3*)
Moderate AD	34	34 (1*)	35 (2*)	103(3*)
Severe AD	33 (2*)	34 (2*)	32	99 (4*)
total	100 (3*)	99 (3*)	99 (4*)	298 (10*)

*dropped out

Abbreviations: AD, Alzheimer's disease.

Table 2. Comparison of demographic characteristics, main medicines received, and assessments among groups of participants with Alzheimer's disease (mean±SD)

	Music therapy group (Group A, n=97)	Lyrics controlled therapy group (Group B, n=96)	Control group (Group C, n=95)
Age, years	68.9±7.1	70.3±8.3	69.9±7.9
Male gender, n	40	39	39
Education, years	6.70±3.01	6.82±3.13	6.71±2.89
Main medicines			
Acricept	17	17	18
Rivastigmine	15	16	14
Memantine	27	25	26
Atypical antipsychotics	9	11	12
MMSE score			
t_0	13.45±3.66	13.12±3.71	13.22±4.01
t_1	13.34±3.82	12.98±3.99	12.99±3.85
t_2	13.34±4.00	12.83±3.56	12.98±4.15
WHO-UCLA AVLT			
Immediate recall			
t_0	5.43±1.41	5.55±1.46	5.77±1.63
t_1	6.06±1.56	5.86±1.71	5.34±1.90
t_2	5.93±1.75	6.15±1.86	5.80±1.55
Delayed recall			
t_0	4.68±1.99	4.72±1.11	4.74±1.20
t_1	4.91±1.06	4.70±1.36	4.64±1.18
t_2	4.73±1.10	4.59±1.42	4.65±1.31
Verbal fluency test			
t_0	5.51±1.11	5.62±1.36	5.53±1.34
t_1	5.85±1.04*	5.92±1.54*	5.48±1.86
t_2	5.78±1.09*	5.68±1.37	5.41±1.51
NPI score			
t_0	26.18±13.25	24.79±12.42	25.62±13.21
t_1	20.00±12.63*	21.85±11.34*	24.99±12.35
t_2	19.36±12.24*	22.08±12.01	25.22±11.38
Caregiver distress			
t_0	31.77±13.64	32.60±15.67	31.95±15.02
t_1	20.71±11.95*	28.41±12.19	30.21±11.54
t_2	20.31±11.44*	29.38±12.82	30.87±12.75
Barthel Index			
t_0	38.83±14.35	38.17±13.61	38.58±10.75
t_1	39.71±13.23	37.54±10.29	38.02±11.44
t_2	39.79±12.94	37.83±11.01	38.52±12.18

Note: Group A=Music therapy group; Group B= Lyrics controlled therapy; Group C= Control group; t_0=baseline; t_1=3 months; t_2=6 months

* compared with either of the other two groups using one-way ANOVA and LSD or the Pearson Chi-square test, $P<0.05$

Abbreviations: MMSE, Mini Mental State Examination; WHO-UCLA AVLT, World Health

Organization University of California-Los Angeles, Auditory Verbal Learning Test; NPI, Neuropsychiatric Inventory.

Table 3 Comparison of neuropsychological tests and activities of daily living among groups of participants with mild Alzheimer's disease (mean±SD)

Item (mean±SD)	Group A（*n*=32）	Group B（*n*=31）	Group C（*n*=30）
MMSE score			
t_0	17.55±4.21	17.34±4.50	18.09±4.80
t_1	17.64±5.30	17.57±4.1	17.91±3.1
t_2	17.81±4.70	17.59±5.67	17.95±4.70
WHO-UCLA AVLT			
Immediate recall			
t_0	6.81±1.40	6.90±1.27	6.67±1.09
t_1	7.38±1.45*	6.93±1.34	6.63±1.26
t_2	7.24±1.42	6.92±1.44	6.61±1.13
Delayed recall			
t_0	5.88±1.34	5.88±1.22	5.77±1.25
t_1	6.51±1.52*	5.88±1.26	5.57±1.10
t_2	6.01±1.63	5.69±1.40	5.55±1.30
Verbal fluency test			
t_0	7.62±1.70	7.68±1.76	7.67±1.76
t_1	8.63±1.94*	8.58±1.75*	7.54±2.03
t_2	8.45±1.69*	7.89±1.74	7.43±1.52
NPI score			
t_0	16.37±11.72	13.22±10.26	15.77±11.73
t_1	13.52±11.63	12.65±10.17	15.14±11.58
t_2	13.01±11.72	12.58±10.03	15.42±9.72
Caregiver distress			
t_0	21.71±12.87	22.18±14.34	19.93±13.56
t_1	16.43±11.90	20.44±10.64	19.85±10.59
t_2	15.02±10.56	21.58±11.27	20.46±13.23
Barthel Index			
t_0	50.33±14.14	49.63±15.01	48.94±11.67
t_1	51.42±16.03	47.75±10.31	49.22±13.56
t_2	52.64±14.41	48.72±12.14	48.86±7.92

Note: Group A=Music therapy group; Group B= Lyrics controlled therapy; Group C= Control group; t_0=baseline; t_1=3 months; t_2=6 months

* compared with either of the other two groups using one-way ANOVA and LSD or the Pearson Chi-square test, $P<0.05$

Abbreviations: MMSE, Mini Mental State Examination; WHO-UCLA AVLT, World Health

Organization University of California-Los Angeles, Auditory Verbal Learning Test; NPI, Neuropsychiatric Inventory.

Table 4 Comparison of neuropsychological tests and activities of daily living among groups of participants with moderate Alzheimer's disease (mean±SD)

Item mean±SD	Group A (*n*=34)	Group B (*n*=33)	Group C (*n*=33)
MMSE score			
t_0	13.68±2.19	13.51±3.21	13.44±2.75
t_1	13.60±2.34	13.55±4.01	13.43±3.15
t_2	13.27±3.08	13.43±3.65	13.35±3.72
WHO-UCLA AVLT			
Immediate recall			
t_0	5.24±2.25	5.19±2.41	6.33±2.01
t_1	6.35±1.92	5.23±1.84	5.23±2.11
t_2	6.24±1.42	6.92±1.44	6.61±1.13
Delayed recall			
t_0	4.10±1.44	4.18±1.87	4.32±1.53
t_1	4.13±1.54	4.18±1.78	4.25±1.64
t_2	4.11±1.70	4.19±1.81	4.25±1.63
Verbal fluency test			
t_0	5.33±1.82	5.68±1.55	5.67±1.80
t_1	5.33±1.93	5.65±1.68	5.54±1.96
t_2	5.40±1.74	5.69±1.75	5.43±1.78
NPI score			
t_0	25.68±12.74	23.95±13.32	24.79±14.14
t_1	20.12±11.53	21.36±11.77	23.89±13.54
t_2	19.33±12.25	20.96±12.52	24.24±11.35
Caregiver distress			
t_0	32.85±15.64	32.74±14.63	33.01±15.26
t_1	20.73±10.16 *	28.90±12.90	30.55±19.13
t_2	21.00±13.63 *	29.54±14.86	31.10±13.14
Barthel Index			
t_0	41.21±13.50	40.42±17.32	41.90±13.74
t_1	41.43±16.25	40.71±12.37	40.24±13.36
t_2	40.61±19.42	41.70±14.16	40.84±17.93

Note: Group A=Music therapy group; Group B= Lyrics controlled therapy; Group C= Control group; t_0=baseline; t_1=3 months; t_2=6 months

* compared with either of the other two groups using one-way ANOVA and LSD or the Pearson Chi-square test, $P<0.05$

Abbreviations: MMSE, Mini Mental State Examination; WHO-UCLA AVLT, World Health

Organization University of California-Los Angeles, Auditory Verbal Learning Test; NPI, Neuropsychiatric Inventory.

Table 5 Comparison of neuropsychological tests and activities of daily living among groups of participants with severe Alzheimer's disease (mean±SD)

Item (mean±SD)	Group A (*n*=31)	Group B (*n*=32)	Group C (*n*=32)
MMSE score			
t_0	8.97±4.52	8.64±4.54	8.42±4.72
t_1	8.63±5.10	7.96±4.42	7.91±4.65
t_2	8.80±5.34	7.59±4.86	7.95±4.87
WHO-UCLA AVLT Immediate recall			
t_0	4.20±1.42	4.61±1.27	4.35±1.47
t_1	4.38±1.43	4.63±1.24	4.23±1.22
t_2	4.24±1.63	4.62±1.35	4.21±1.53
Delayed recall			
t_0	4.08±1.42	4.14±1.25	4.20±2.31
t_1	4.11±1.24	4.08±1.35	4.17±1.96
t_2	4.08±1.25	4.07±1.32	4.21±1.14
Verbal fluency test			
t_0	3.54±1.31	3.48±1.34	3.37±1.57
t_1	3.54±1.44	3.63±1.75	3.50±1.55
t_2	3.43±1.41	3.54±1.70	3.49±1.37
NPI score			
t_0	36.87±16.85	36.85±17.63	35.72±15.68
t_1	26.57±10.35*	31.27±15.36	35.35±16.45
t_2	25.96±14.23*	32.43±15.31	35.43±14.36
Caregiver distress			
t_0	40.96±16.46	42.54±13.75	42.13±14.36
t_1	25.12±13.30*	35.64±17.04	39.57±16.34
t_2	25.02±13.47*	36.78±13.47	40.38±17.31
Barthel Index			
t_0	24.35±14.36	24.75±13.14	25.43±12.11
t_1	23.17±15.43	24.38±14.25	25.24±13.20
t_2	25.64±14.34	23.28±14.74	26.44±12.78

Note: Group A=Music therapy group; Group B= Lyrics controlled therapy; Group C= Control group; t_0=baseline; t_1=3 months; t_2=6 months

* compared with either of the other two groups using one-way ANOVA and LSD or the Pearson Chi-square test, $P<0.05$

Abbreviations: MMSE, Mini Mental State Examination; WHO-UCLA AVLT, World Health Organization University of California-Los Angeles, Auditory Verbal Learning Test; NPI: Neuropsychiatric Inventory.

Figure 1

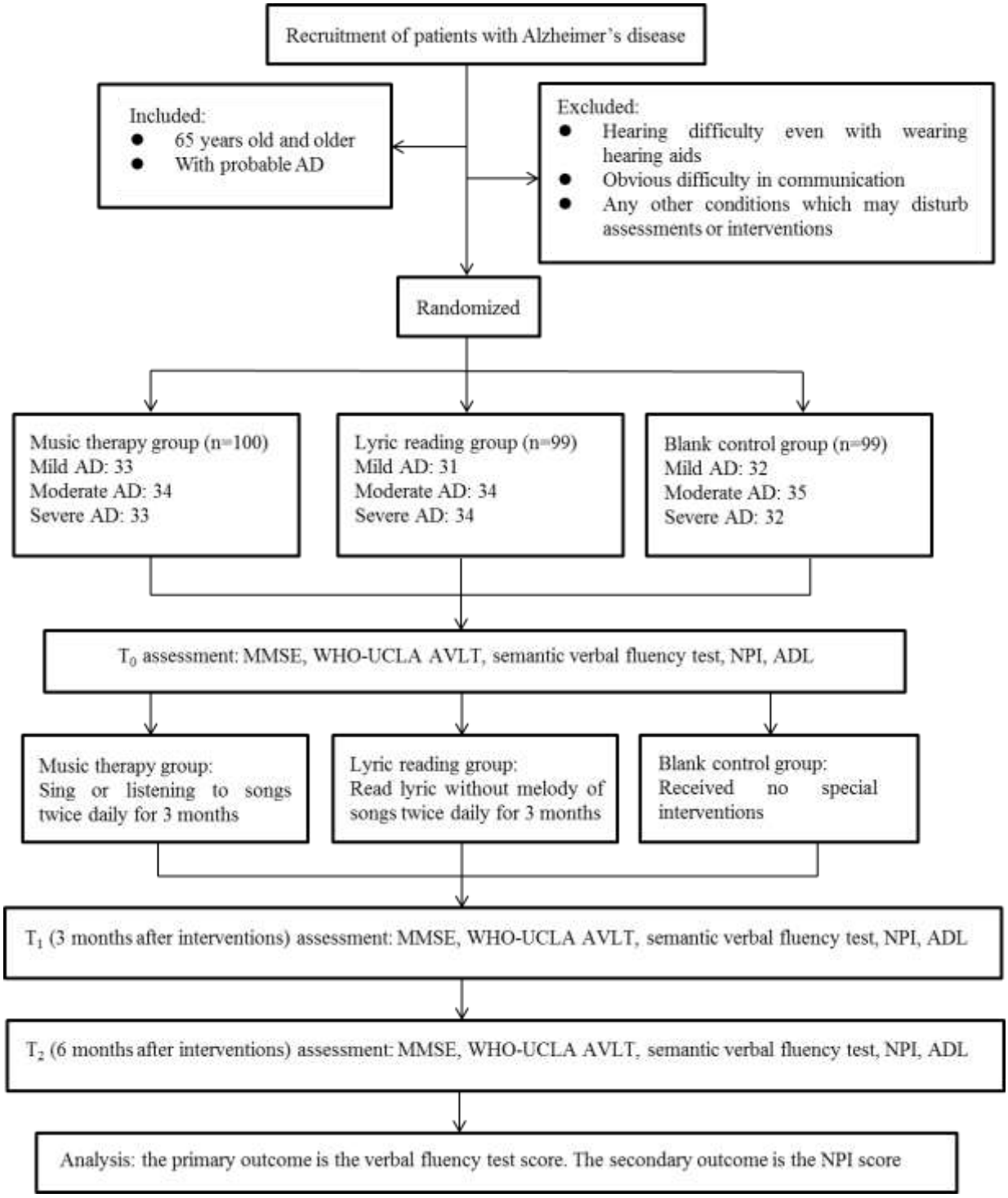

Fig. 1 Overview of participant flow

Abbreviations: AD, Alzheimer's disease; MMSE, Mini Mental State Examination; WHO-UCLA AVLT, World Health Organization University of California-Los Angeles,

Auditory Verbal Learning Test; NPI, Neuropsychiatric Inventory; ADL, activities of daily living.