博士論文

Auditory-Cognitive training improves brain plasticity and cognitive function in the healthy older adults

(聴覚刺激を用いた認知介入が脳可塑性および認知機能に及ぼす影響)

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Summary

The number of older adults is increasing globally. Aging is associated with cognitive and sensory decline. Age-related hearing loss causes speech perception problems and has been linked to cognitive decline. Additionally, declined auditory performance and cognitive function affect the quality of life of older adults. Therefore, it is important to develop an intervention method to improve both auditory and cognitive performances. A previous study reported that a combination of auditory and cognitive (AC) training is more beneficial than a single auditory or cognitive training; however, the study did not directly measure auditory abilities using objective measures, such as the pure-tone audiometry (PTA) threshold. In addition, a suitable active control group was not included in the study. The current study aimed to investigate the beneficial effects of AC training on auditory ability and cognitive functions in healthy older adults. Considering the unresolved issues of the previous study, I focused on the following points in this study: 1) objective auditory measures, such as PTA, were used, 2) an active control group was included a randomize controlled study, and 3) sound volume was manipulated for auditory factor difficulty during training. Fifty healthy older adults were randomly divided into four training groups—an AC training group, an auditory training group (A training), a cognitive training group (C training), and an active control group. Cognitive function measures (digit-cancellation test [D-CAT]; logical memory [LM]; digit span), auditory measures (PTA), and magnetic resonance imaging (MRI) measures were evaluated before and after the training periods. I did not find any statistically significant beneficial effects of AC training on cognitive and auditory performance compared to that of other training modalities (A training group, C training group, and active control group). Compared to other groups, the AC training group showed differences in regional gray matter volume (rGMV) in the right dorsolateral prefrontal cortex, the left inferior temporal gyrus (L. ITG), the left superior frontal gyrus, the left orbitofrontal cortex, the right cerebellum (lobule 7 Crus 1).

According to PTA findings, the auditory training factor groups (ATFGs, the AC and A training groups) improved in auditory measures compared to the non-ATFGs (the C training group and active control group). The ATFGs showed an increase in rGMV and FC in the left temporal pole compared to the non-ATFGs. The cognitive training factor groups (CTFGs; the AC and C training groups) showed statistically significant improvement in cognitive performances in terms of LM and D-CAT results compared to the non-CTFGs (A training group and active control group). AC training significantly changed rGMV in brain regions related to attention and memory. These results suggest that older adults can listen to sound with low volume after auditory training (ATFGs), and cognitive training (CTFGs) improved their attention and episodic memory performance. In addition, AC training led to changes in brain structure related to cognitive and auditory processes. Therefore, the present study newly developed AC training would be useful in enhancing the quality of life of older adults.

1.Introduction

1.1. Age-Related Hearing Loss

Aging is associated with cognitive and sensory decline (Deal et al, 2017). The incidence of age-related hearing loss (ARHL) has been increasing among older adults worldwide. Hearing loss has become a public health problem with the burgeoning aging population (WHO, 2011).

ARHL is characterized by degeneration of the mechanotransducing inner and outer hair cells of the cochlea as well as the auditory nerve (neural presbycusis) (Schuknecht & Gacek, 1993; Ohlemiller, 2004). In addition to peripheral lesions, changes are likely to occur in the central auditory pathways, and these contribute to the development and progression of ARHL (Jayakody et al, 2018).

ARHL is a multifactorial disorder with several underlying risk factors, such as age, environment, and lifestyle (Yamasoba et al, 2013). ARHL causes speech perception problems (Lin, 2011) and has been linked to consequent decline in cognitive function (Deal et al, 2017), increased social isolation (Mick et al, 2014), reduced quality of life (Li et al, 2014), increased risk of depression (Li et al, 2014), and decline in ability to independently perform activities of daily living (Dalton et al, 2003).

Epidemiological evidence across populations suggests that cognitive decline with ARHL is a risk factor for the development of dementia in older adults (Taljaard et al, 2016). A meta-analysis study concluded that cognitive function and hearing impairment were correlated and that hearing loss affected multiple cognitive domains (Taljaard et al, 2016).

1.2. Hearing aid in older adults

Hearing aids are the first choice for individuals with hearing loss, and there have been considerable advances in the digital technology used in hearing aids over the last two decades

(Sarant et al, 2020). A hearing aid is a small electronic device that people wear in or behind their ear (Hearing Loss Association of America: https://www.hearingloss.org/hearing-help/technology/hearing-aids/).

Although satisfaction with hearing aids has improved, users often encounter difficulties in challenging listening conditions (May et al, 1990; Ohlenforst et al, 2017). The disadvantages of hearing aids include inability to block background noise and to separate speech from sounds in noisy environments; additionally, they do not allow users to hear sounds at a distance (Ohlenforst et al, 2017).

1.3. Auditory training in older adults

Auditory training aims to improve wide range of auditory processes, such as recognition, discrimination, identification, and comprehension (Olson, 2015). Auditory training is usually provided in a face-to-face setting. It involves active engagement with sounds, including syllables, words, phrases, sentences, and connected discourse (Musiek et al, 2014) and helps participants learn to distinguish between systematically presented sounds (Schow & Nerbonne, 2006).

Typically, auditory training studies ask participants to listen to a target sound stimuli with white noise during training (Karawani et al, 2016). In previous auditory training study (Karawani et al, 2016), healthy older adults and older adults with ARHL were asked to perform three types of trainings under adverse listening conditions (speech-in-noise, time-compressed speech, and competing speakers). After a 4-week-training period, compared to a control group, the group of participants that received auditory training showed improvements in auditory performance measured by a speech-in-noise pseudoword discrimination task and speech-in-noise sentences task.

The traditional auditory training approach has a limitation. Participants often get bored during training because they passively listened to a sound. Participants often do not complete the traditional auditory training (Levitt et al, 2011). Moreover, these negative emotions affect motivation to continue to training tasks (Pekrun et al, 2010; Rowe & Fitness, 2018). Previous studies have reported that participants feel highly motivated and enjoy simple cognitive training tasks, such as mathematical calculations (Nouchi et al, 2012a; 2016). Therefore, I hypothesized that auditory training with a cognitive task could enhance motivation to continue auditory training.

Previous auditory training studies showed auditory performance with noise (Pichora - Fuller et al, 1995). It is important to listen to words or sentence with noise in daily life. However, older adults have difficulty with low sound volume (Slade et al, 2020). Therefore, it is important to investigate whether auditory training improves auditory performance in a low sound volume (least audible sound). Previous studies on auditory training have reported that auditory training had a beneficial effect on trained auditory performance categories (Karawani et al, 2016). For example, after auditory training, in which participants were required to listen to a target sound stimulus with white noise, participants showed improvements in the trained auditory performance categories, such as speech-in-noise situation, but not other auditory performance categories, such as speech comprehension (Karawani et al, 2016). It indicates that auditory performance in low sound volume situations would be improved if I used auditory training using a low sound volume situation compared with a subjective comfortable listening level. Therefore, in this study I manipulated sound volume compared with subjective comfortable listening level for auditory training.

1.4. Relationship between auditory abilities and cognitive resources

Speech comprehension involves the perceptual sensitivity of the peripheral nervous system and the language-specific cognitive abilities of the central nervous system (Sommers, 1997). Success in achieving listening goals may depend on the distribution of greater cognitive functions of the listeners and the quality of the signals (Pichora-Fuller, 2016). Therefore, it is important to consider the aspects of both hearing and cognitive functions.

Multiple factors (such as hearing loss and decline in cognitive function) contribute to speech recognition difficulties (Wayne & Johnsrude, 2015). ARHL affects the central auditory system and increases deficits in auditory processing, which negatively affects auditory perception and speech communication performance (Ouda et al, 2015).

Uhlmann and colleagues (Uhlmann et al, 1989) proposed that sensory deprivation may contribute to a subsequent decline in cognitive function. Sensory deprivation may degrade the sensory information needed for proper cognitive function (Schneider et al, 2002). Moreover, sensory deprivation may reduce the extent of social interaction with an associated effect on cognitive function (Lin et al, 2013).

Conversely, cognitive abilities are critical under less favorable listening conditions and are sensitive to change with age. When a speech signal is poorly processed, it is transmitted from the ear to the brain, and greater cognitive resources may be required to interpret the meaning of the sound than would be with a properly processed sound (Schneider et al, 2010). However, the increased demands of auditory processing deplete a listener's limited cognitive resources pool, leaving few resources available for other complex tasks, such as language comprehension, memory, walking, and driving (Schneider et al, 2010). Thus, there is no guarantee that increasing cognitive energy will solve hearing problems. Therefore, success in achieving auditory goals may depend on the considerable cognitive energy expenditure that is required when the quality of the signal available to the listener is suboptimal.

When decline in cognitive functions and ARHL are comorbid, communication difficulties increase and induce stress and fatigue. These communication difficulties can also exacerbate dementia-related behavioral problems, such as apathy, depression, and aggression, in older adults (Palmer et al, 2017).

Perceptual declines in older adults are highly associated with declines in cognitive function (Baltes & Lindenberger, 1997). Thus, auditory ability and cognitive functions are also likely to support speech recognition. Therefore, a combination of auditory and cognitive training (AC training) is recommended to achieve listening goals.

1.5. Combination of auditory and cognitive trainings

Recently, a type of AC training has been proposed (Yusof et al, 2019). Yusof used AC training to improve speech recognition, auditory processing, and cognitive abilities in older adults with normal cognitive and mild cognitive impairment (Yusof et al, 2019).

Yusof used five adaptive training tasks (word-in-noise, sentence-in-noise, word span, word order, and word position). Two tasks (word-in-noise and sentence-in-noise) were categorized as auditory training, and three tasks (word span, word order, and word position) as AC training. For example, in the word span task, participants had to identify all words (primary task) in the presence of cognitive interferences (secondary task). In the primary task, the participants had to select pictures that the words presented to them and this selection could be in any order. Cognitive interference (secondary task) consisted of simple questions with four multiple-choice answers. The cognitive interference task was introduced once the participants mastered a word span level of five words in the primary task. The secondary task was introduced either before or after the primary task. The participants had to listen to the primary stimuli as an auditory training task and perform the secondary stimuli as a cognitive training task. After 8 weeks' of AC training, improvements in general cognitive functions measured by

Montreal Cognitive Assessment and auditory processing ability measured by a dichotic digits test was observed in older adults with normal cognition and neurocognitive impairment compared to that of a control group.

A previous study reported that AC training had positive effects on cognitive and auditory functions (Yusof et al, 2019). However, some limitations were noted. First, they did not directly measure auditory abilities using objective auditory assessment measures, such as the pure-tone audiometry (PTA) threshold. Second, they did not use a suitable active control group. In the previous study, the control group participants were asked to watch documentary programs on history and literature using the same device used for AC training (Yusof et al, 2019). This ensured that the control and training groups matched in terms of training duration and the auditory stimuli received. However, it is unclear which components of the auditory and cognitive aspects are important for improving cognitive and auditory performance. Third, the previous study used different signal-to-noise-ration in order to change the difficulty of the task (Yusof et al, 2019). Although it is important to listen to the words and sentences with noises (Pichora - Fuller et al, 1995), older adults usually show difficulty with low sound volume (decibel [dB]) (Slade et al, 2020).

1.6. Experimental design of the current study

The present study was designed to evaluate the beneficial effects of AC training on hearing ability and cognitive and brain functions in healthy older adults. I conducted a single-blinded randomized controlled trial using an AC training group, an auditory (A) training group, a cognitive (C) training group, and an active control group.

Considering the abovementioned shortcomings of the previous studies, I used objective auditory measures (PTA) to assess auditory abilities. Moreover, to resolve the issue with the active control group, I used an active control group that eliminated the need for change in cognitive or auditory training difficulty. Further, I controlled the sound volume to manipulate the auditory factor during training. By controlling the sound volume, I was able to control auditory training factor in the AC and A training groups.

Furthermore, I conducted magnetic resonance imaging (MRI) before and after training to investigate changes in brain plasticity after training.

Additionally, the present study conducted a training period of four weeks. Previous studies of auditory training performed auditory training for four weeks (Karawani et al., 2016). Significant improvements were observed in all training conditions in both the ARHL and normal hearing groups, as mentioned in the section “Auditory training in older adults” (see Section 1.3). Improvements in assessments of cognitive function after 4 weeks of training have been reported in a study of cognitive training in the elderly (Biel et al., 2020). Moreover, the previous AC training study conducted training for eight weeks (Yusof et al., 2019). The participants were evaluated after 4 and 8 weeks of training. Both the normal hearing and hearing loss groups were shown to have improved auditory processing and cognitive function (see Section 1.5). In a cognitive training study, the plasticity of the brain structure was observed after 4 weeks of training (Biel et al., 2020). For this reason, the present study conducted training for four weeks.

1.7. Hypothesis development

This is the first study to use AC training with a lower volume than the subjective comfortable listening level to control the difficulty in auditory training factor. To evaluate the beneficial effect of AC training on auditory ability and cognitive and brain functions in healthy older adults, I used PTA to measure auditory performance, cognitive measures (digit-cancellation test [D-CAT], logical memory, [LM], digit span [DS]), and brain structure and functional connectivity (FC). I proposed the following three hypotheses regarding the behavioral and brain imaging results obtained from each training group.

First, I hypothesized that AC training would show a superior beneficial effect on cognitive and auditory performances than would the other training groups because cognitive (tasks difficulty during training) and auditory (sound volume control) factors were changed based on participants' performance. I expected that AC training would alter regional gray matter volume (rGMV) and FC related to cognitive and auditory processes. For example, I expected changes in brain regions, such as the bilateral temporal cortex (speech perception) (Peelle, 2019), the temporal pole (TP), and the precuneus, that are related to auditory processes (high listening effort) (Olson et al, 2007; Rosemann & Thiel, 2019). Moreover, I expected changes in brain regions, such as the dorsal attention network (DAN) (Sanchez-Perez et al, 2019), prefrontal regions (Nissim et al, 2017), and medial temporal lobe (MTL), that are related to high cognitive processes (Tsukiura et al, 2002).

Second, I hypothesized that the auditory training factor groups (ATFGs; the AC and A training groups) would show improvement in auditory performance and changes in the abovementioned auditory process-related brain regions.

Third, I hypothesized that the cognitive training factor groups (CTFGs; the AC and C training groups) would show improvements in cognitive performance and changes in the abovementioned cognitive process-related brain regions.

2. Methods

2.1. Ethics Statement

The study was performed in accordance with the Declaration of Helsinki (1991). All participants provided written informed consent prior to enrollment, and the Ethical Committee of Tohoku University Graduate School of Medicine approved this study.

2.2. Randomized Controlled Trial Design

This study was registered in the UMIN Clinical Trial Registry (UMIN000042271). It was conducted between August 2019 and December 2019 in Sendai City, Miyagi Prefecture, Japan.

Participants were informed that the study was designed to investigate the effects of four training programs. The researchers who were not involved in generating the randomization sequence enrolled eligible participants and conducted pre-assessments. These participants were then randomly assigned to receive combination training (AC training group), single training (A training group or C training group), and no training (active control group). The random allocation sequence was generated using an online computer program (http://www.graphpad.com/quickcals/). All participants engaged in their assigned training during in-person visits for 4 weeks. After training, the participants completed the post-training outcome assessments (Figure 1 and Figure 2).

2.3. Participants

Fifty-six participants (13 men and 43 women; mean age = 68.07 years [standard deviation, SD = 4.14]) were recruited from the general population through advertisements in a local town paper and local newspapers (Kahoku Weekly). Interested participants were screened using a semi-structured telephone interview (10 questions) that took approximately 10 min.

The 10 questions pertaining to the inclusion and exclusion criteria were related to (1) age, (2) sex, (3) previous experience in intervention studies, (4) native language, (5) handedness, (6) subjective memory function, (7) history of medication use and disease (including hearing-related problems), (8) blood pressure, (9) history of diabetes, and (10) ability to complete training schedule. The participants were then invited to visit Tohoku University. I collected written informed consent from 55 participants (one participant did not visit the institution on the first day). Subsequently, all participants were subjected to a detailed auditory assessment (including assessment of PTA threshold and speech reception threshold [SRT]), cognitive function tests (such as the Mini-Mental State Examination [MMSE], LM, DS, and D-CAT), and MRI. None of the participants were excluded based on MMSE scores. However, two participants declined to participate before they were randomized into groups. One participant was excluded based on the auditory assessment (profound unilateral hearing loss), one participant was excluded because the MRI examination criteria were not met, and two participants declined to participate after initiating training (Figure 1).

2.4. Auditory measures

2.4.1. Overview of auditory assessment

All participants underwent auditory assessment before starting the training schedule and after completing the eight training sessions at Tohoku University in a soundproof room. The PTA air conduction thresholds were measured using an audiometer (AA-76, RION, Tokyo, Japan) and standard headphones (AD-06B). The audiometer was calibrated in dB hearing level according to standards of the International Organization for Standardization (1996) and the American National Standard Institute (2004). Before PTA, all participants underwent an otoscopic examination to exclude occluded ear canals or other irregularities (i.e., no tympanic membrane abnormalities were observed). Each ear was assessed. More details follow below.

2.4.2. Pure-tone audiogram

PTA threshold measurements were conducted for conventional audiometric frequencies of 150 Hz, 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz, and 8 kHz. According to the Japanese standards, measurements at 3 kHz and 6 kHz were not included. The assessment was started with the right ear. The data for the better ear were included as outcome measures in the analysis. The Japan Audiological Society used audiological criteria for normal hearing (<25 dB) and mild (25–39 dB), moderate (40–69 dB), severe (70–89 dB), and profound hearing loss (≥90 dB).

2.4.3. Speech recognition thresholds

The SRT is the lowest hearing level at which 50% of the words presented can be identified correctly. The goal is to find SRT assessment, the softest sound level at which one can hear and repeat correctly approximately one-half of the compound words heard. The guidelines of the Japan Audiological Society recommend using single-digit numbers for the measurement (2 "ni," 3 "san," 4 "yon," 5 "go," 6 "roku," and 7 "nana"). The single-digit numbers were created and used to measure the threshold for listening to speech-by-speech (speech understanding threshold). The participants were asked to write the single-digit number that they heard.

2.4.4. Speech discrimination test

A speech discrimination test assesses how well a participant can discriminate words. In this test, the participants heard words through headphones at a dB level louder than their SRT. This test used monosyllabic sounds (e.g., /a/, /e/ singular vowels and /ka/, /ki/) to measure the intelligibility (speech discrimination) of speech sounds. The participants were asked to write down the monosyllabic words presented to them. The percentage of correct answers represented the results of the speech discrimination test. Successful repetition of 90% or more words is considered excellent.

2.4.5. Hearing Handicap Inventory for the Elderly

I subjectively measured hearing performance using the Hearing Handicap Inventory for the Elderly (HHIE) (Ventry & Weinstein, 1982; Hajime, 1994). The HHIE is designed to measure whether there are restrictions in activities of daily living faced by participants due to hearing impairments. The HHIE contains items involving embarrassment, irritability, frustration, self-worth and depression, changes in activities, and communication (Figure 3).

2.5. Cognitive function measures

2.5.1. Overview of cognitive function assessment

Cognitive function was divided into four categories: general cognition, episodic memory, working memory, and attention. Global cognitive status was measured using the MMSE (Folstein et al, 1975). Episodic memory was measured using LM (Wechsler, 1987). Working memory was measured using DS (Wechsler, 1997). Attention was measured using D-CAT (Hatta et al, 2000). More details follow below.

2.5.2. Mini-Mental State Examination

The MMSE (Folstein et al, 1975) is a widely used cognitive function test among older adults. MMSE scores indicate global cognitive function. It contains tests of orientation, attention, memory, language, and visual-spatial skills. The MMSE is a 20-item instrument, and it is scored from 0 to 30. Lower scores (<26) indicate the degrees of general cognitive dysfunction. The primary measure was the total score of this assessment (max = 30).

2.5.3. Logical Memory

LM evaluates episodic memory. It is a subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987). LM consists of two short-paragraph stories (Story A and Story B). In LM, participants were asked to memorize these short stories. They were scored in terms of the number of story units recalled, as specified in the WMS-R scoring protocol. I used either Story A or Story B. The primary measure for this task was the number of correct story units recalled.

2.5.4. Digit Span

DS is a subtest of the Wechsler Adult Intelligence Scale-Third Edition. DS measures working memory by requiring participants to memorize numbers and repeat the numbers in inverse order. For DS, participants repeated numbers in the same order as they were read aloud by the examiner. The examiner read a series of number sequences that the examinee had to repeat in either forward or reverse order. DS has 16 sequences. This test’s primary measures are raw scores that reflect the number of correctly repeated sequences until the discontinue criterion (i.e., failure to reproduce two sequences of equal length) is met (Wechsler, 1997). The maximum raw score of DS is 16.

2.5.5. Digit Cancellation

D-CAT evaluates attention (Hatta et al, 2000). Each test sheet for D-CAT consists of 12 rows of 50 digits. Each row contains five sets of numbers from 0 to 9 arranged in a random order. Consequently, any digit appears five times in each row with randomly determined neighbors. D-CAT comprises three such sheets. The participants were instructed to search for the target number (s) specified and to delete each one with a slash mark as quickly and as accurately as possible until a stop signal was sent. There were three trials: first with a single target number (6), second with two target numbers (9 and 4), and third with three (8, 3, and 7). Each trial lasted for 1 min. Consequently, the total time required for D-CAT was 3 min. In the second and third trials, I emphasized that all the target numbers should be canceled without omission. The primary measure of this test is the number of hits (correct answers). I used only the number of hits in the first trial.

2.6. Brain imaging assessment

To acquire MRI data, I used a 3.0 Tesla Philips Achieva MRI scanner (Philips, Amsterdam, The Netherlands) with an eight-channel head coil at the Institute of Development, Aging and Cancer, Tohoku University. Fifty participants performed MRI before and after assessment. They were instructed to avoid moving their head. High-resolution T1-weighted structural images (240 × 240 matrix, time repetition [TR] = 6.6 ms, time echo [TE] = 3 ms, field of view [FOV] = 24 cm, slices = 162, and slice thickness = 1 mm) were collected using a magnetization-prepared rapid gradient-echo sequence. The quality of all imaging data was checked visually. The total scan time was 8 min. For the resting-state parameter, I used 34-transaxial gradient-echo images (64 × 64 matrix, TR = 2000 ms, TE = 30 ms, flip angle = 70° , FOV = 24 cm, and slice thickness = 3.75 mm) covering the entire brain and acquired using an echo-planar sequence. For this scan, 160 functional volumes were obtained, while the participants were resting. The total scan time was 6 min. I utilized the same parameters as those used in a previous laboratory study (Takeuchi et al, 2012). During resting-state scanning, the participants were instructed to keep their eyes closed, stay as motionless as possible, not fall asleep, and avoid thinking about anything in particular.

2.7. Inclusion and exclusion criteria

The following participants were included: those who self-reported being right-handed, those who were native Japanese speakers; those who were unconcerned about their memory function; those who were not taking medications that interfered with cognitive function (such as benzodiazepines, antidepressants, and other central nervous system agents); those who did not have a history of diseases that affect the central nervous system, including thyroid disease, multiple sclerosis, Parkinson’s disease, stroke, severe hypertension (systolic blood pressure >180 mmHg and diastolic blood pressure >110 mmHg), and diabetes; and those who were >60 years old. Participants who had participated in other cognitive or auditory intervention studies were excluded. Participants with an MMSE score of <26 (Folstein et al, 1975) or those with moderate-to-profound hearing loss were also excluded.

2.8. Four training groups

I set four training groups (AC training, A training, C training, and active control groups) (Table 1). All training groups performed three cognitive training tasks (short-term memory, working memory, and attention training tasks) with volume controlled audio stimuli (Figure 4). Each cognitive training task had 4 task difficulty levels as a cognitive training factor (from level 1 [easy] to level 4 [difficult]). Sound volume of auditory stimulus had 4 levels as an auditory training factor (from level 1 [easy] to level 4 [difficulty]).

The AC training group underwent a combination of cognitive and auditory training. In this group, the levels of the cognitive and auditory training factors were changed at the same time from level 1 to level 4 depending on the participants’ performance.

In the A training group, the auditory training factor varied from level 1 to level 4 depending on the participants’ performance. However, the cognitive training factor was not changed. The participants completed the three cognitive training tasks at level 1 difficulty of the cognitive training factor.

In the C training group, the cognitive training factor varied from level 1 to level 4 depending on the participants' performance. However, the auditory training factor did not change. The participants completed the three cognitive training tasks at level 1 of the auditory training factor.

In the active control group, there were no variations in the cognitive or auditory training factors. The participants completed the three cognitive training tasks at level 1 of cognitive and auditory training factors in all the training sessions.

2.9. Criteria of level change of cognitive and auditory training factors

I checked the participants' performance after each session. Levels of cognitive and auditory training factors were changed in every training session. The training level was increased when performance was >70%; it was maintained when the performance on the training tasks was 50%–70% and was decreased by one level when the performance was <50%.

2.10. Details of three cognitive training tasks

2.10.1 Manipulation of sound volume of auditory stimulus

All three cognitive training tasks used auditory stimulus. In the first session, all participants completed the three cognitive training tasks at level 1 of the auditory training factor. The level 1 of the auditory training factor differed among the participants because the level 1 of auditory factor was set based on the SRT at baseline.

For, the C training and active control groups the auditory training factor levels were not changed throughout the training sessions. They completed each cognitive training task at the level 1 of the auditory training factor. In the AC and A training groups, the sound volume of auditory stimuli for each cognitive training task was changed based on the cognitive training performance.

In this study, level 1 sound volume was set at SRT + 3 dB to SRT – 3 dB. Level 2 sound volume was set at SRT + 0 dB to SRT – 6 dB. Level 3 sound volume was set at SRT – 3 dB to SRT –9 dB. Level 4 sound volume was set at SRT – 6 dB to SRT – 12 dB.

2.10.2 Working memory training task

Working memory training included the most commonly used listening span training. Participants listened (via headphones) to numbers and then recalled all numbers in inverse order. The recall was made orally and recorded. There was no time limit for responding. The subsequent trial started only when the participant pressed a button. If all digits in a trial were recalled in the correct order, then the trial was given a score of 1; if the response was incorrect in any way, then the trial was assigned a score of 0. In one training session, the participants performed all tasks three times for each task for 5 min (Figure 5A). Level 1 of cognitive training was composed of three numbers. Level 2 was comprised four numbers. Level 3 was composed of five numbers, and level 4 of six numbers.

2.10.3 Short-term memory training task

Short-term memory training was performed using a word recall task. After listening to each list of words, the participants were asked to recall all the words they could remember from the list in the same order. The recall of each trial was recorded. If all words were repeated in the correct order in a trial, then a score of 1 was given; if the response was incorrect in any way, then the trial was assigned a score of 0. In one training session, the participants performed all the tasks three times for 5 min (Figure 5B). Level 1 was composed of three words. Level 2 comprised four words. Level 3 included five words, and level 4 was composed of six words.

2.10.4 Attention training task

In the attention training task (go/no-go attention task), the participants were presented one spoken vowel (i.e., /a/) through headphones. The participants were instructed to press a "red button" key as quickly as possible each time a specific target vowel was presented. The response time (RT) and number of correct responses were recorded. In one training session, the participants performed the task three times for 5 min (Figure 5C). Level 1 comprised one vowel and one target. Level 2 was composed of two vowels and one target. Level 3 involved three vowels and two targets. Level 4 was consisted of four vowels and two or three targets.

2.11. Task stimuli

I recorded the voices of two female and two male Japanese speakers. They were recorded while they read a worklist from an A4 format sheet (Table 2). The recording consisted of numbers (e.g., "1" /ichi/, "2" /ni/, "3" /san/, "4" /yon/, "5" /go/, "6" /roku/, "7" /nana/, "8" /hachi/, and "9" /kyu/), polysyllabic words with high-frequency (e.g., "table" /tsukue/), and vowels (e.g., /a/, /e/, /i/, /o/, and /u/). They were asked to maintain a flat tone of voice and pronounce the items as clearly as possible. If an experimenter judged that the recorded items were not easily discriminable, they asked the speakers to repeat them until they were. The voice was recorded in a "wav" file format using the Audacity software (https://www.audacityteam.org/) at the rate of 44.100 samples per second with a Panasonic laptop computer (CF-RZ). Sixteen bits were allocated to each sample. Each speaker was recorded in a soundproof room and used an omnidirectional AT2020USB+PK microphone (Audio-Technica, Tokyo, Japan). The microphone was positioned approximately 2.5 cm from the speaker's mouth while maintaining a microphone-to-mouth angle of approximately 90°. The mean duration of each stimulus was 2–8 ms. Each number and word were pronounced slowly (normal speed). I used the word list from a previous study by NTT Basic Research

Laboratories (Amano et al, 1995). All audio stimuli were presented to both slides at once via headphones (BOSE QC 35 II).

The training sessions involved three tasks (working memory, short-term memory, and attention training tasks). All training tasks were controlled using E-Prime 3.0 software, and information on oral responses, button presses, and RT were collected. When starting the training session instructions regarding each task were shown on a screen (white letters on black background). A trial started when the participants agreed and pressed a button to proceed. Each trial started with a central fixation point (5 ms duration), followed by a presentation of audio stimuli (audio stimuli varied depending on each task's difficulty level). After the audio stimuli were presented, a screen with instructions on how to answer was presented (for working memory training task: "Repeat what you heard in inverse order. When finished, press the red button to proceed."; for the short-term memory training task: "Repeat what you heard in the same order. When finished, press the red button to proceed."). The subsequent trial started only after the participants pressed the red button. In the working memory and short-term memory training tasks, the participants' oral responses were recorded. After the instruction screen, a central fixation point was presented for the attention training task while an audio stimulus was played. All participants were instructed to press a button while listening to the audio stimulus, and they were instructed to respond as accurately and as quickly as possible. The participants used their right hand to press the button.

2.12. Training session schedule and setup

Each training session involved approximately 1 hour of training per day and was conducted 2 days per week for four weeks, resulting in a total of 8 sessions in a predetermined order. The examiner and participants contacted each other by telephone in case of health problems (rescheduling the training date) and delays on the training session day. On the training day, it was possible to train two participants simultaneously for one hour (two soundproof rooms were available). The second participant started training with a delay of 5 min. The 5-min delay was computed in the setup. Before entering the soundproof room, the examiner asked the participants to turn off their cell phone if they had one. The participant sat in front of a personal computer screen at a distance of approximately 60 cm, and a microphone was positioned approximately 20 cm from the participant's mouth. The participant was required to press a previously assigned response key button with the right hand or to respond orally when necessary. The correct placement of the headphones was confirmed each time by the examiner. Between each training sub-session, there was a 5-min break. Each sub-session consisted of one trial of each task.

2.13. Experimental setup

Training sessions were carried out in two soundproof rooms (YAMAHA Corporation). During the session, each acoustic soundproof room was occupied by one participant. The internal dimensions of the soundproof room were 1.766 mm × 2.648 mm. Within each soundproof room, a table and chair were positioned in the center. To maintain air circulation inside the room, a portable fan was placed. The table had a 40-inch display, a keyboard, a mouse, headphones (BOSE QC 35 II), a microphone, and an audio volume control system. To adjust the audio volume in increments of 0.5 dB, the Grace Design m905 system (Grace Design Corporation) was used. The examiner controlled the session outside the soundproof room. Therefore, all USB cables (keyboard, mouse, microphone, and audio input volume controller) were connected to a 4-port adapter with a 5 m-extension cable. The monitor HDMI cable was connected similarly. The extension cables passed through an opening of the soundproof room and were connected to a laptop (MOUSE B505H-S1). Outside the soundproof room, a trained examiner was responsible for guiding each participant's training session. To maintain cleanliness during the training sessions, the examiner sterilized the keyboard, mouse, microphone, chair, and table with alcohol after each session. A metal plate was placed in front of the microphone to comply with hygiene requirements (Figure 6).

2. 14. Behavioral data analysis

Table 3 presents the baseline characteristics of the participants. I calculated the changes in scores (post-assessment score minus pre-assessment score) for all cognitive function tests and auditory assessments. Cognitive function measures and auditory measures were dependent variables. I used a two (the auditory training factor: with, without) by two (the cognitive training factor: with/without) factorial analysis covariance (ANCOVA) with permutation tests to investigate significant group differences in each cognitive function measure and auditory measure. All analyses were preformed using the "aovp" function of the "lmPerm" package for changes in scores associated with each cognitive measure and auditory measure. I used the permutation ANCOVA test because it is suitable for small sample analysis and is freely distributed. Therefore, the permutation ANCOVA test is suitable and sufficiently powered for present study (Kulason et al, 2018). The changes in scores in each group (AC training group, A training group, C training group, and active control group) were the dependent variables. All pre-assessment scores of the dependent variables, sex, age, and MMSE were used as covariates to adjust for background characteristics and exclude the possibility of any pre-existing difference in measures between the groups affecting the result. Fifty randomly allocated participants were included in the analyses. The level of significance was set at $p < 0.05$. The PTA threshold was the primary outcome. I applied the Bonferroni–Holm procedure (Holm, 1979) separately for cognitive measures (LM, D-CAT, and DS findings) and auditory measures (PTA threshold). All analyses are performed using the R software (R Core Team, 2019) (R Core Development Team, Toulouse, France).

Additionally, participants in the active control group performed the baseline (level 1) in all sessions. In the behavioral analysis, I excluded the effect of active control on behavioral measures. Therefore, I excluded the possibility that the effect of active control had an impact on any outcome.

2. 15. Brain image data analysis

2. 15.1. Image preprocessing of structural brain image

As a first step, I reviewed and converted all pre- and post-Digital Imaging and Communication in Medicine scans into the Neuroimaging Informatics Technology Initiative format using MRICRON software before running the analysis. All imaging data were analyzed using Statistical Parametric Mapping 12 (SPM12; Wellcome Department of Cognitive Neurology; London, UK) implemented in MATLAB (Mathworks Inc.; Natick, MA, USA). Briefly, SPM12 and Computational Anatomy Toolbox 12 (CAT12) (http://www.neuro.uni-jena.de/cat/) were used to create an asymmetric diffeomorphic anatomical registration through exponentiated Lie (DARTEL) algebra template from the original and flipped gray matter and white matter segments. T1-weighted structural images of each participant (pre- and post-imaging data) were segmented and normalized to the Montreal Neurological Institute (MNI) space using CAT12 to generate images with $1.5 \times 1.5 \times 1.5$ mm^3 voxel size diffeomorphic anatomical registration through the DARTEL registration process. Moreover, I performed volume change correction (modulation). I used a SPM12 image calculator (ImCalc) to calculate the post-imaging value minus pre-imaging value for all participants. The required mask expression was $(i2 - i1).*(i2 > 0.1).*(i1 > 0.1)$. The mask expression was used to restrict the statistical analysis to regions of the brain expected to contain true signals. Subsequently, the generated rGMV image was smoothed using a Gaussian kernel of 8-mm full width at half maximum (FWHM). (Figure 6)

2. 15. 2. Brain structural statistical analysis

Full factorial model analysis was performed using SPM12 and CAT12. This approach was used to analyze the superior effects of AC training compared to other training groups, the effect of the auditory training factor (with/without), and the cognitive training factor (with/without). The main effects of both the factors and group comparisons were used as contrasts of interest (cognitive training factor main effect: AC + C > A + active control; auditory training factor main effect: AC + A > C + active control; the superior effects of AC training compared to other training groups: AC > A + C + active control). The model included two levels of each factor (cognitive and auditory training factors), age, sex, and total intracranial volume as covariates. Additionally, in the analysis of the superior effects of AC training compared to other training groups, I included the mask images (AC > C, AC > A, and AC > active control, a threshold of $p < 0.05$, uncorrected). The covariates were mean centered, and I used threshold-free cluster enhancement (TFCE) with randomized (5.000 permutations) nonparametric testing using the TFCE toolbox (http://dbm.neuro.uni-jena.de/tfce/). I applied a cluster-level FWE-corrected $p < 0.05$. (Figure 6)

2. 15. 3. Preprocessing and analysis of resting-state functional connectivity

Resting-state FC preprocessing and analysis were performed using a standard pipeline in the CONN toolbox (Whitfield-Gabrielli and Nieto-Castanon, 2012), implemented in MATLAB. Preprocessing included realignment, direct segmentation, normalization to the MNI space (2 mm^3), outlier detection (artifact detection tool based identification of outlier scans for scrubbing; motion correction = 0.9 mm; global-signal z-value threshold = 5) (https://www.nitrc.org/projects/artifact_detect), and smoothing (FWHM = 8 mm). The realignment and scrubbing parameters and the BOLD signal from the WM and cerebrospinal fluid were regressed using a general linear model. Data were band-pass filtered at 0.008–0.09 Hz to reduce the effects of low-frequency drifts and high-frequency noise. First-level analyses included the calculation of individual whole-brain seed-to-voxel FC maps.

2. 15. 4. Resting-state functional connectivity of analysis

For second-level analysis, in the group-level comparisons, seed-based FC maps were used to analyze the superior effects of AC training compared to other training groups (AC > A + C + active control), main effect of the auditory training factor, and main effect of the cognitive training factor. I included the mask expression (AC > C, AC > A, and AC > active control, a threshold of $p < 0.05$, uncorrected). The brain seed regions were selected with reference to the results obtained in the brain structure analysis. I used threshold-free cluster enhancement (TFCE) with randomized (5.000 permutations) nonparametric testing using the TFCE toolbox (http://dbm.neuro.uni-jena.de/tfce/). The clusters were threshold at an FWE corrected at $p < 0.05$ using a cluster-forming threshold of $p < 0.001$, which was uncorrected.

3. Results

3.1. Behavioral data

All participants had normal cognitive function, as indicated by MMSE scores (mean = 28.88, standard deviation [SD] = 1.22), and a normal to mild PTA threshold according to the Japan Audiological Society (mean = 19.23, SD = 2.95). Cognitive and auditory assessment scores before and after training in all groups are presented in Figure 8.

First, to investigate whether a group difference existed at the baseline, I performed a two (the auditory training factor: with/without) by two (the cognitive training factor: with/without) ANCOVA with permutation tests for the baseline data. I did not find statistically significant interaction between the auditory and cognitive training factors (LM [F (1, 44) = 0.49, $p = 0.63$, adjusted $p = 0.85$], D-CAT [F (1, 44) = 0.17, $p = 0.64$, adjusted $p = 0.85$], DS [F (1, 44) = 0.65, $p = 0.51$, adjusted $p = 0.85$], PTA [F (1, 44) = 3.25, $p = 0.08$, adjusted $p = 0.48$]). I did not find any significant effect of the auditory training factor (LM [F (1, 44) = 0.02, $p = 0.96$, adjusted $p = 0.96$], D-CAT [F(1, 44) = 0.04, $p = 0.60$, adjusted $p = 0.48$], DS [F(1, 44) = 0.96, $p = 0.23$, adjusted $p = 0.58$], PTA [F(1, 44) = 1.50, $p = 0.17$, adjusted $p = 0.58$]), and the main effects of the cognitive training factor (LM [F (1, 44) = 0.91, $p = 0.26$, adjusted $p = 0.58$], D-CAT [F (1, 44) = 1.12, $p = 0.9$, adjusted $p = 0.96$], DS [F (1, 44) = 1.37, $p = 0.29$, adjusted $p = 0.58$], PTA [F (1, 44) = 0.021, $p = 0.96$, adjusted $p = 0.96$]). The results indicated that the cognitive functions and auditory performance at baseline did not differ among the groups.

Second, I investigated effects of the interventions on cognitive function and auditory performance using the ANCOVA for changes in scores. I did not find statistically significant beneficial effects of AC training on PTA thresholds (F [1, 43] = 0.72, $p = 0.27$, adjusted $p = 0.40$), LM (F [1, 42] = 0.19, $p = 0.38$, adjusted $p = 0.49$), D-CAT scores (F [1, 42] = 2.30, $p = 0.06$, adjusted $p = 0.17$), and DS (F [1, 42] = 0.28, $p = 0.92$, adjusted $p = 1.00$) compared to other training groups. However, I found statistically significant main effects in the factor groups. In terms of cognitive functions, the CTFGs (the AC and C training groups) had improvements in LM (F [1, 42] = 5.15, $p = 0.009$, adjusted $p = 0.04$) and D-CAT scores (F [1, 42] = 7.2, $p = 0.006$, adjusted $p = 0.04$) compared to the non-CTFGs. Moreover, the ATFGs (the AC and A training groups) had improved auditory performance (F [1, 42] = 3.12, $p = 0.02$, adjusted $p = 0.06$) compared to the non-ATFGs.

3.2. Brain image results

3.2.1. Brain structural results

Only the AC training group showed changes in the AC training showed differences in rGMV in the right dorsolateral prefrontal cortex (R. DLPFC), the left inferior temporal gyrus (L. ITG), the left superior frontal gyrus (L. SFG), the left orbitofrontal cortex (L. OFC), and the right cerebellum (lobe 7 Crus 1) (FWE corrected at $p < 0.05$, Figure 8 and Table 4). In addition, the ATFGs showed changes in the cluster located in the left temporal pole (L. TP) compared to the non-ATFGs (FWE corrected at $p < 0.05$, Figure 9A and Table 4). Differences were observed in the clusters located in the right inferior occipital gyrus (R. IOG), right cerebellum (lobule 7 Crus 1) and R. ITG between the CTFGs and non-CTFGs (FWE corrected at $p < 0.05$, Figure 9B and Table 4).

3.2.2. Brain functional connectivity results

The brain seed regions were selected based on the results obtained from the brain structure analysis. Thus, the AC training group showed no statistically significant changes compared to the other training groups. Compared to the non-ATFGs, the ATFGs had significantly increased FC between the TP and precuneus (Figure 11, Table 5). Compared to the non-CTFGs, the CTFGs showed no statistically significant changes compared with the other training groups.

4. Discussion

4.1. Summary of results

In this study, I investigated the beneficial effect of AC training on cognitive functions (via LM, D-CAT, and DS), auditory performance (via PTA), and MRI measures (brain structure and FC) and compared it to other training groups (A training group, C training group, and active control group) in healthy older adults. This is the first study to investigate the effects of an auditory training factor (audio volume control stimuli) on the improvement of speech perception and changes of brain structure and FC. Additionally, it is the first to find the effect of AC training on neuroimaging measures.

I found two results (behavioral results and brain image results) for each analysis (AC training compared to other training groups, the ATFGs compared to non-ATFGs, and the CTFGs compared to non-CTFGs) (Table 6). First, the ATFGs had improved auditory performance (PTA threshold) compared to non-ATFGs. The CTFGs showed improved cognitive performance in terms of LM and D-CAT compared to non-CTFGs. Second, in the structural brain, the AC training led to a change in rGMV in the frontal regions compared to other groups. The ATFGs changed rGMV in the L. TP compared to non-ATFGs. Moreover, the ATFGs increased the FC between the L. TP and the precuneus compared to non-ATFGs. In terms of CTFGs, the rGMV changed in the R. DLPFC, the L. ITG, the OFC, and the right cerebellum (lobule 7 Crus 1) compared to non-CTFGs. I have discussed these findings separately below.

4.2. The ATFGs improved auditory measures compared to non-ATFGs and the CTFGs improved cognitive measures compared to non-CTFGs

I did not find any statistically significant beneficial effects of AC training on cognitive function and auditory performance compared to other training groups. This result is inconsistent with previous findings (Yusof et al, 2019). The training duration might be one of the reasons for this inconsistency as the previous study had an 8-week intervention period, while present study had a 4-week intervention period. Second, I did not find any statistically significant beneficial effects of AC training on cognitive function and auditory performance when compared to other training groups; however, when I compared the results of the changed scores (post minus pre-training) on the measures (see figure in Appendix section), I observed that AC training increased the most after training. Previous MRI studies with first-time learners of Japanese have measured how brain activity changes after only a few months of studying a new language (Sakai et al., 2021). However, Sakai showed that the participants' changes in brain activation did not show improvement in behavioral performance compared to pre-training measures accuracy. Therefore, plastic changes in the brain occur first, followed by behavioral changes.

The ATFGs (the AC and A training groups) had improved auditory performance (PTA threshold), and as discussed later, changed rGMV related speech perception, and increased brain connectivity in regions related to listening effort and language processing compared to the non-ATFGs. These findings support second hypothesis in the present study. As previously reported, older adults can discriminate between words and sentences in high noise situations after a 4-week training period (Karawani et al, 2016). However, the current study is the first to report that older adults can listen to a sound with low volume as shown by the PTA threshold.

The CTFGs (the AC and C training groups) showed improved cognitive performance in terms of LM and D-CAT compared to the non-CTFGs. As discussed later, I also found significant increases in rGVM in the R. ITG, the R. IOG, and the right cerebellum (lobule 7 Crus 1) in the CTFGs compared to those of the non-CTFGs. These results support third hypothesis in present study. Multiple cognitive training usually presented better results when compared with single cognitive training (Auffray & Juhel, 2001). Previous studies that used cognitive training reported near transfers in cognitive function (Golino et al, 2017). They used an intervention characterized by attention, episodic memory, and working memory training. Their results showed positive effects for intervention training involving Picture Completion, Digit Symbol-Coding, and Digit (Golino et al, 2017), which is consistent with present study results.

4.3. The AC training, the ATFGs and the CTFGs induced neural plastic changes in the brain

I did not find any statistically significant beneficial effects of AC training on cognitive function and auditory performance compared to the other training groups. However, AC training-induced neural plastic changes in the brain, which were not observed in the other training groups. Brain imaging results showed an increase in rGMV in the R. DLPFC, the L. ITG, the OFC, and the right cerebellum (lobule 7 Crus 1). The DLPFC is suggested to be involved in central executive processes (Hertrich et al., 2021). Although the DLPFC may have multiple functions and executive processes have diverse processes, particularly relevant to multiple tasks, the DLPFC is involved in scheduling processes in complex tasks (task management) (Smith & Jonides, 1999). Moreover, these results are consistent with previous findings using multitasking cognitive training study (two or more cognitive activities at the same time). A multitasking cognitive training using an auditory stimulus and a visual stimulus tasks increased rGMV in the DLPFC in healthy young adults after 4 weeks training period (Takeuchi et al, 2014). Although the functional imaging literature on dual-task (more than one task at a time) performance to the recruitment of prefrontal (Szameitat et al, 2002; Tombu et al, 2011; Nijboer et al, 2014) that are typically implicated in situations requiring effortful control (Vincent et al, 2008; Duncan, 2010; Niendam et al, 2012). Additionally, previous neuroimaging studies reported that the OFC, ITG, and the cerebellum (lobule 7 Crus 1) are important for integration of visual and auditory information (Wu et al, 2013; Nogueira et al, 2017; Lin et al, 2020). The OFC, like other regions in the prefrontal cortex, is thought to play an important role in adaptation to goal-directed behavior (Furuyashiki & Gallagher, 2007). During AC training, the participants had to integrate multisensory information during the combination of the auditory and cognitive training factors. Therefore, rGMV in the R. DLPFC, the L. ITG, the OFC, and the right cerebellum (lobule 7 Crus 1) was increased after 4 weeks of AC training.

The ATFG brain imaging results showed an increase in rGMV in the left TP compared to non-ATFGs. Auditory information is processed in a temporal sequential pattern. Auditory storage and a temporal readout of sequential auditory information from memory are critical for organizing auditory stimuli into auditory-image units (Massaro, 1972). Without such faithful temporal storage of raw fine-structure signals of the leading wave, neither the central computation of the similarity (correlation) nor the perceptual integration between the leading and lagging waves is possible. Therefore, this faithful auditory storage of the raw fine-structure signals has been termed primitive auditory memory and recognized as the early point of auditory short-term memory system (Huang et al., 2009; Li et al., 2013).

A previous fMRI study used sentence-listening tasks in normal hearing and listening difficulty between 6 and 12 years (Stewart et al., 2020). They used three contrasts (phonology, intelligibility, and semantics). The phonology contrast showed bilateral activation in the middle and superior temporal gyrus, including Heschl's gyrus and TP. Phonology is a system of processing the smallest units of speech sounds and their linguistic combinations. In accordance with previous findings (Khalfa et al., 2001), the TP descending influence may improve the auditory afferent message by adapting the hearing function according to the cortical analysis of the ascending input. The previous and current studies showed that listening under adverse conditions increases the activity of the anterior temporal cortex regions, specifically in the TP.

In the present study, the participants in the ATFGs required auditory effort because the sound volume decreased during the auditory training task.

In terms of FC, the ATFGs (the AC and A training groups) showed a significant increase in FC between the L. TP and precuneus compared to the non-ATFGs. The FC between the TP and precuneus is reportedly important in hearing sound in situations requiring high auditory effort (Rosemann & Thiel, 2019). A study has suggested that FC between the TP and precuneus was associated with auditory effort (Rosemann & Thiel, 2019). In the ATFGs (the AC and A training groups), participants focused on low sound volume during auditory training tasks. Therefore, FC between the L. TP and the precuneus was compared between the ATFGs and non-ATFGs.

The CTFGs (the AC and C training groups) showed a significant increase in rGMV in the R. ITG, the R. IOG, and the right cerebellum (lobule 7 Crus 1) compared to the non-CTFGs. Previous functional neuroimaging study, the L. ITG should be recruited more for the maintenance of words than pseudowords (Fiebach et al, 2006). In studies of language processing, the ITG has also associated with prelexical processing of abstract word form (Cohen et al, 2000) and with conceptual semantic processing (Herbster et al, 1997), independent of presentation modality (Cohen et al, 2004). The previous training study supports the suggestion that the cerebellum may be important for shifting performance from attentionally demanding stage to a more automatic state (Holtzer et al, 2017). Previous neuroimaging studies reported that the ITG and the cerebellum (lobule 7 Crus 1) are associated with information integration (Wu et al, 2013; Nogueira et al, 2017; Lin et al, 2020). Additionally, a previous study has reported that activity occurs in the IOG during tasks that require episodic memory usage (Matthaus et al, 2012). The brain imaging results showed an increase in rGMV in the R. ITG, the R. IOG, and the right cerebellum (lobule 7 Crus 1). The participants in the CTFGs (the AC and C training groups) were required to exert more cognitive effort as the cognitive training tasks increased in difficulty.

4.4. Limitations, future studies, and implications

The present study had some limitations. First, AC training had fewer beneficial effects on behavioral performance compared to other training modalities. However, I found positive effects on the brain structure and FC. A possible explanation for this could be the training period. The present study training period is consistent with previous studies on auditory training and cognitive training (Nouchi et al., 2012b; 2014; Walden & Khayumov, 2020). However, it was insufficient for AC training, and the benefits of the combined training were not demonstrated in the assessments performed. Second, I did not consider the effects that could occur over time after training. It would be beneficial if a future study would consider the long-term effects of AC training. Third, the present study did not evaluate the beneficial effects of training on quality of life. As mentioned previously, ARHL causes a cascade of deficits that can lead to dementia. Thus, after the present training, the participants may have affected communicating in quality of life and change in social isolation. It would be beneficial if a future study would consider the quality of life effects of AC training. Fourth, this was a limitation of the behavioral analysis. The PTA threshold was the primary outcome. Thus, I applied the Bonferroni-Holm procedure separately for cognitive measures (LM, D-CAT, and DS) and auditory measures (PTA threshold). However, when the Bonferroni-Holm test was applied to all four measurements, no significant results were observed. Fifth, if the performance of the active control group also improved after one month, participation in the active control group may have contributed to the improvement. The possibility of continuing to take some training may improve the performance. Moreover, although the difficulty level of the tasks appeared to be easy, the participants of each group did not reach the last level of training in the high hit percentage score. Therefore, the method used did not reach the maximum level of training. However, the training groups reached more than 50 percent of performance success (see table in the Appendix section).

5. Implications

Hearing aids are the first choice for people with hearing loss and have made significant technological advances over the last two decades. Although satisfaction with hearing aids has improved, hearing aid users often encounter difficulties in challenging listening conditions (Ohlenforst et al., 2017). The disadvantages of hearing aids include the following:1) they do not block background noise, 2) separate speech from sounds in noisy environments, and 3) they allow users to hear sounds at a distance (Ohlenforst et al., 2017). Thus, current AC training has important implications for the clinical management of people with deterioration in auditory and cognitive processing. The present study used auditory-cognitive training to increase auditory and cognitive function. Even in situations of poor listening quality, the subject would be able to perform listening processing without interfering with the performance of other cognitive functions. AC training changed the brain structure in the DLPFC and ITG, which are associated with working memory and auditory processing, respectively. I believe that this study has implications for improving auditory performance and cognitive function in older adults. In addition, the results reported here demonstrate a new method to train auditory and cognitive processes simultaneously. This method may be beneficial for older adults with declining auditory and cognitive abilities. Moreover, the present training method may improve auditory sensitivity and alter brain structure and functional connectivity.

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Figures and Tables

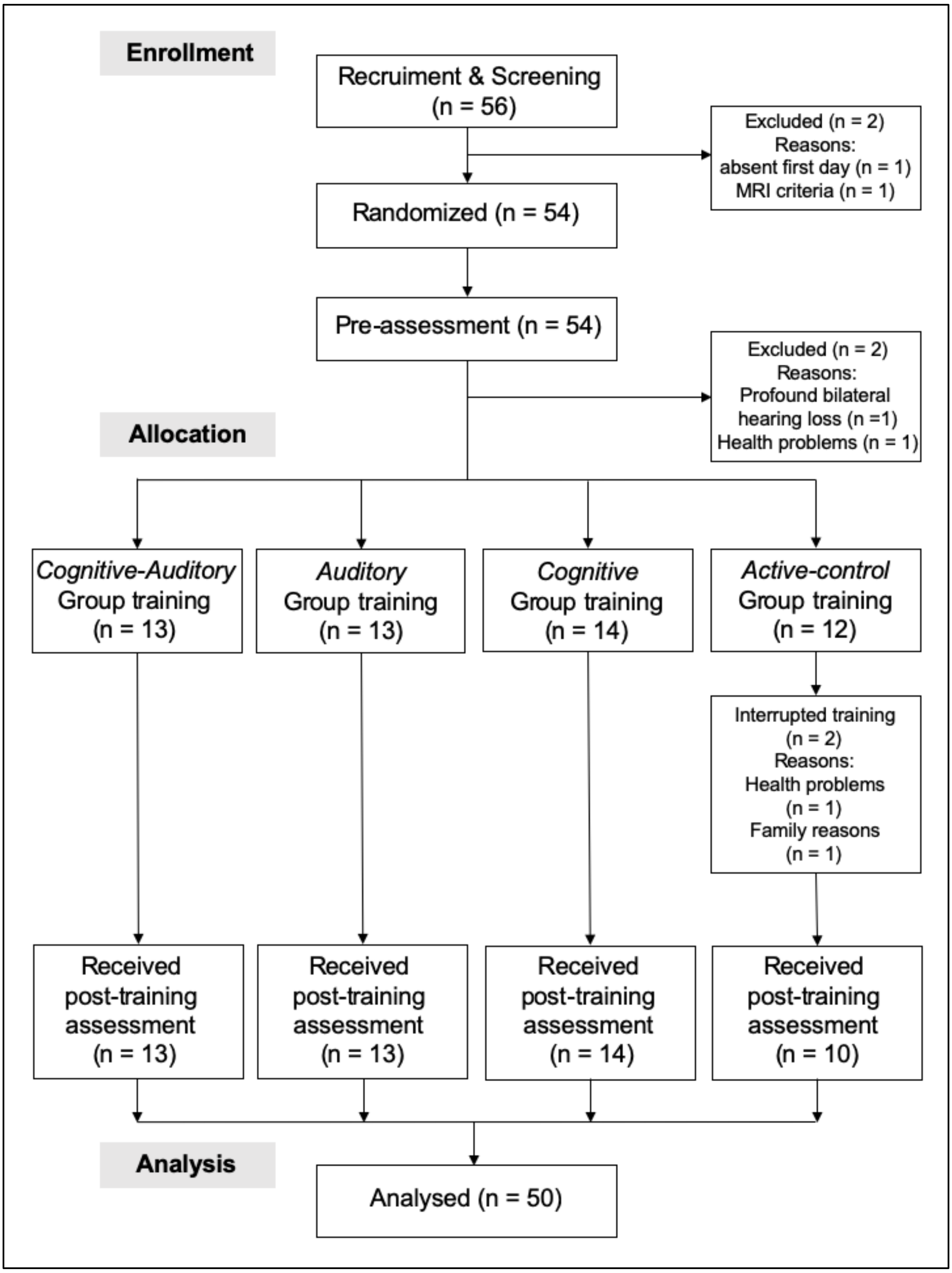


Figure 1. CONSORT flowchart.

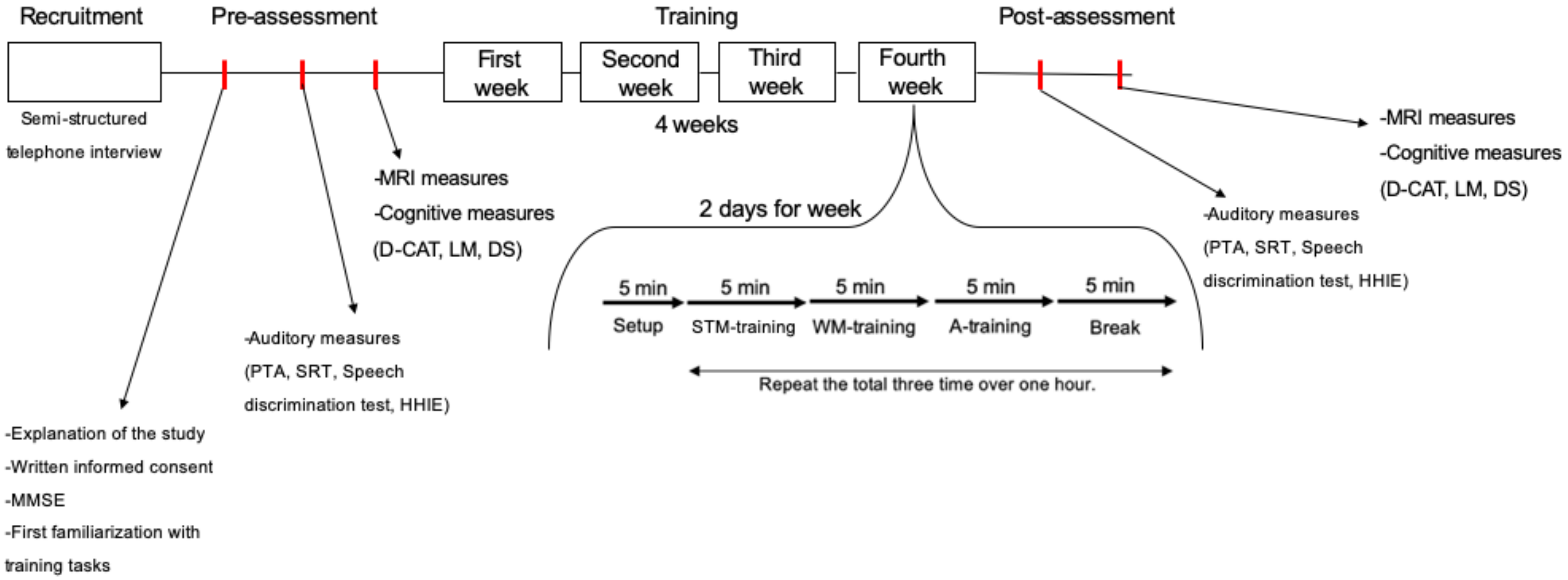
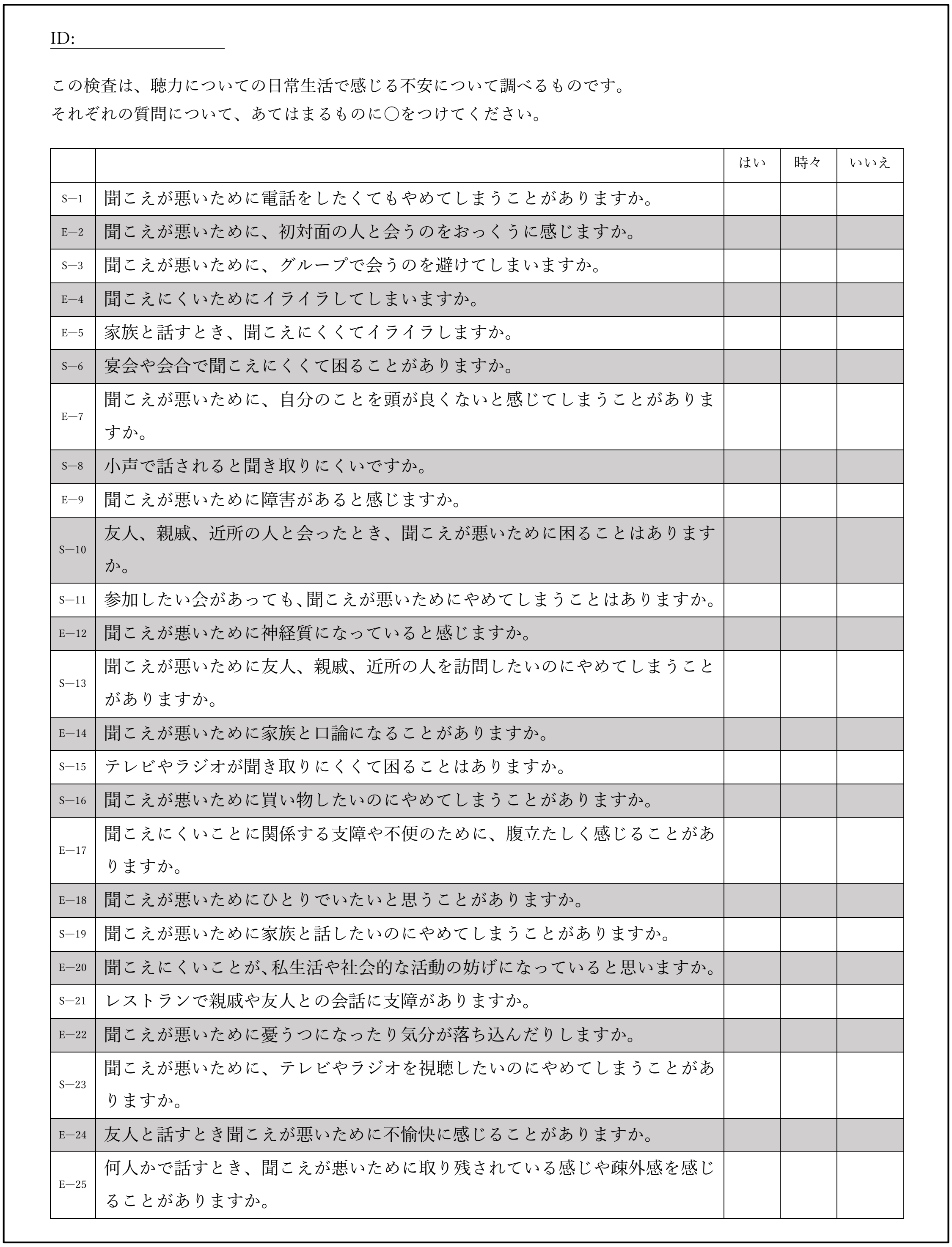


Figure 2. Timelines and phases of the study.



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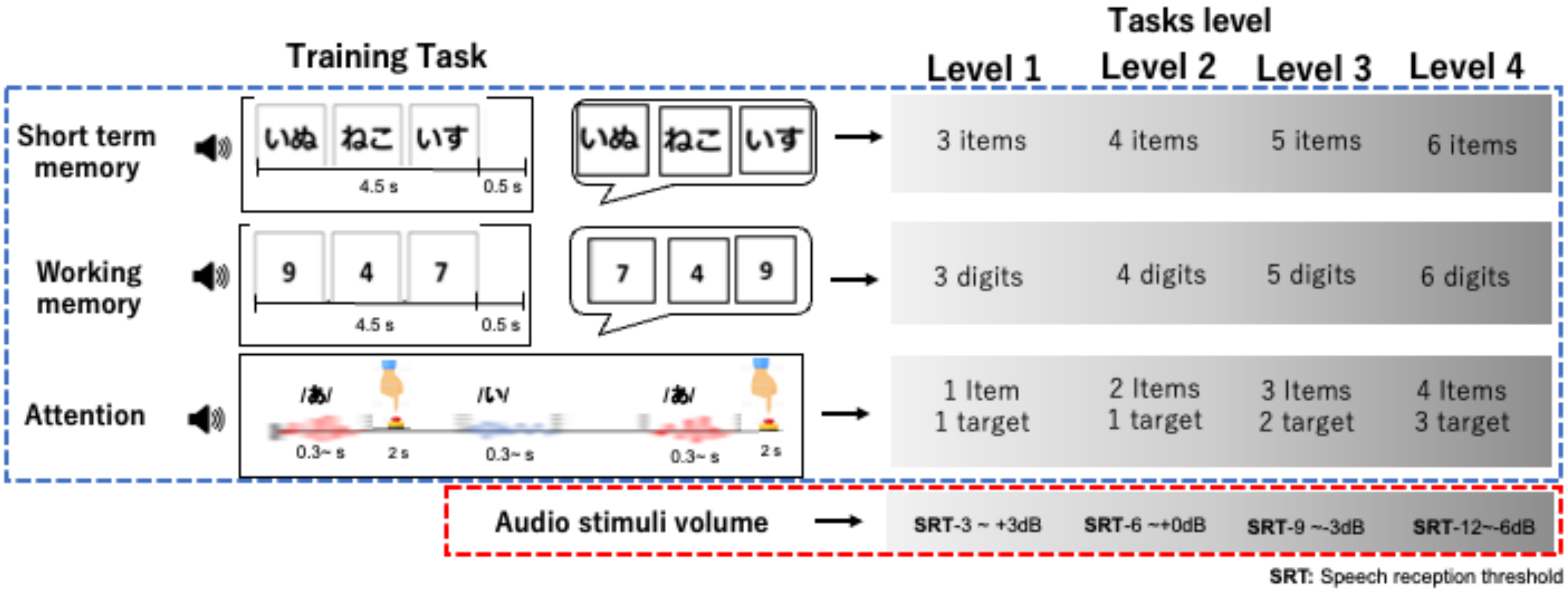
この検査は、聴力についての日常生活で感じる不安について調べるものです。
それぞれの質問について、あてはまるものに〇をつけてください。

		はい	時々	いいえ
S−1	聞こえが悪いために電話をしたくてもやめてしまうことがありますか。			
E−2	聞こえが悪いために、初対面の人と会うのをおっくうに感じますか。			
S−3	聞こえが悪いために、グループで会うのを避けてしまいますか。			
E−4	聞こえにくいためにイライラしてしまいますか。			
E−5	家族と話すとき、聞こえにくくてイライラしますか。			
S−6	宴会や会合で聞こえにくくて困ることがありますか。			
E−7	聞こえが悪いために、自分のことを頭が良くないと感じてしまうことがありますか。			
S−8	小声で話されると聞き取りにくいですか。			
E−9	聞こえが悪いために障害があると感じますか。			
S−10	友人、親戚、近所の人と会ったとき、聞こえが悪いために困ることはありますか。			
S−11	参加したい会があっても、聞こえが悪いためにやめてしまうことはありますか。			
E−12	聞こえが悪いために神経質になっていると感じますか。			
S−13	聞こえが悪いために友人、親戚、近所の人を訪問したいのにやめてしまうことがありますか。			
E−14	聞こえが悪いために家族と口論になることがありますか。			
S−15	テレビやラジオが聞き取りにくくて困ることはありますか。			
S−16	聞こえが悪いために買い物したいのにやめてしまうことがありますか。			
E−17	聞こえにくいことに関係する支障や不便のために、腹立たしく感じることがありますか。			
E−18	聞こえが悪いためにひとりでいたいと思うことがありますか。			
S−19	聞こえが悪いために家族と話したいのにやめてしまうことがありますか。			
E−20	聞こえにくいことが、私生活や社会的な活動の妨げになっていると思いますか。			
S−21	レストランで親戚や友人との会話に支障がありますか。			
E−22	聞こえが悪いために憂うつになったり気分が落ち込んだりしますか。			
S−23	聞こえが悪いために、テレビやラジオを視聴したいのにやめてしまうことがありますか。			
E−24	友人と話すとき聞こえが悪いために不愉快に感じることがありますか。			
E−25	何人かで話すとき、聞こえが悪いために取り残されている感じや疎外感を感じることがありますか。			

Figure 3. Hearing Handicap Inventory for Elderly Japanese version (HHIE).



	Auditory-Cognitive training	Auditory training	Cognitive training	Active control
Auditory factor	Level 1 to 4	Level 1 to 4	Level 1	Level 1
Cognitive factor	Level 1 to 4	Level 1	Level 1 to 4	Level 1

Figure 4. Training level in the cognitive training factor (three task training) and auditory training factor (audio volume control stimuli). In the bottom part, the summary table of the training groups. Auditory-cognitive training change difficulty in auditory and cognitive factors, auditory training chance difficulty only in auditory factor, cognitive training change only in cognitive factor, and active control groups no change in any difficulty.

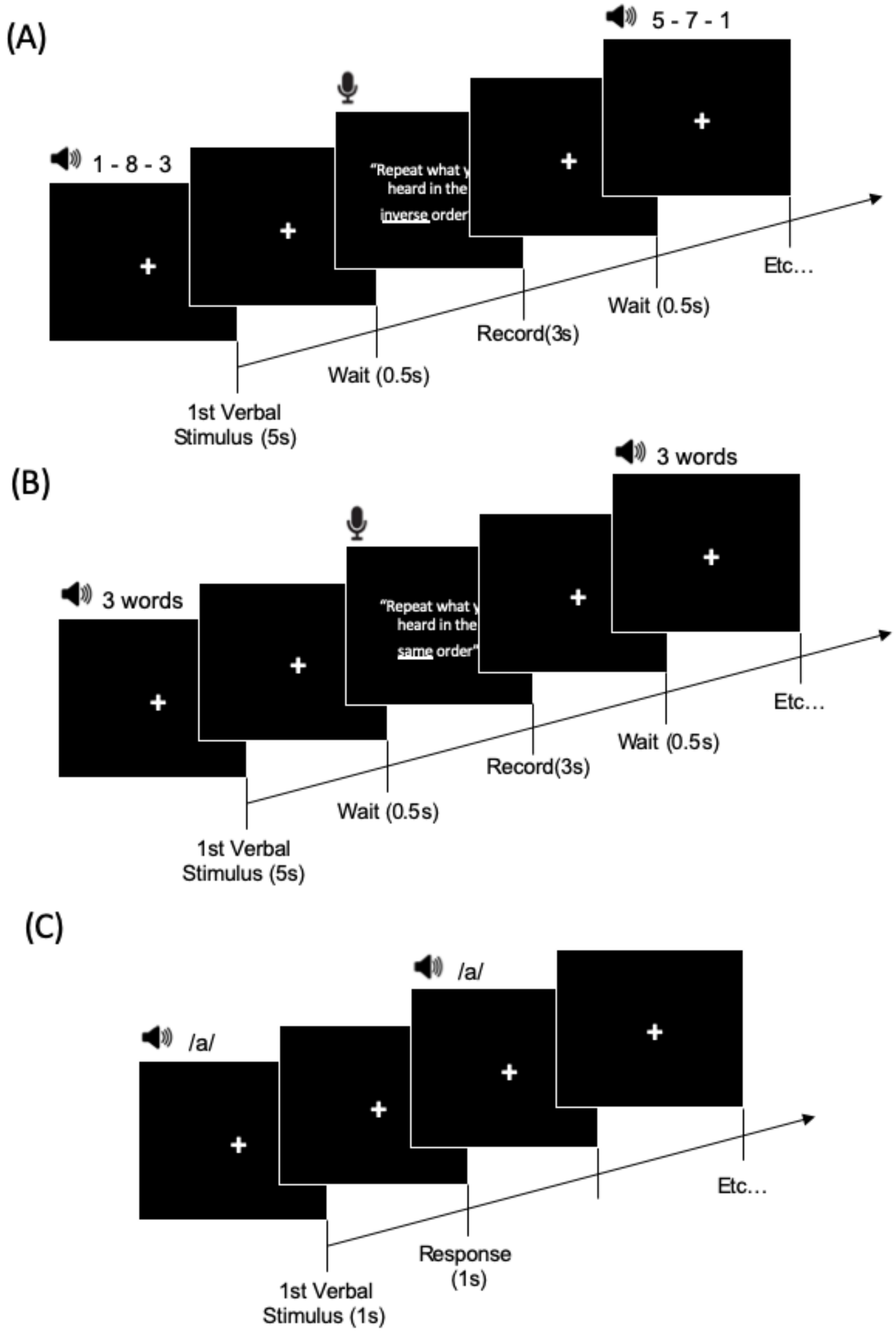


Figure 5. Training task procedure for working memory training task (A), short-term memory training task (B), and attention training task (C).

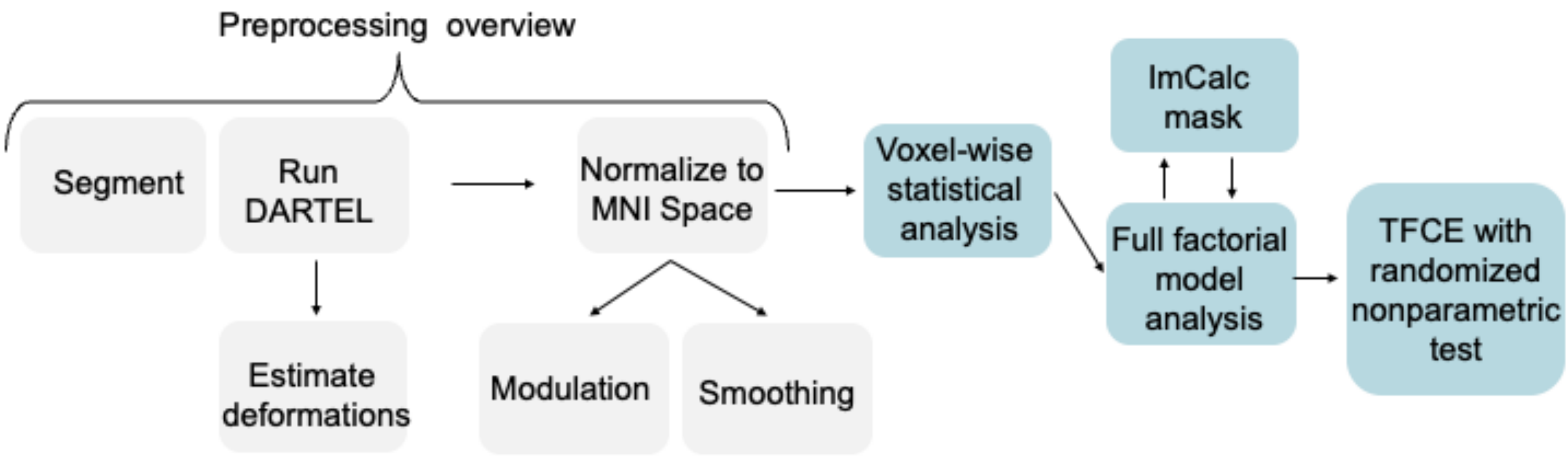


Figure 6. The summary schema of image preprocessing of structural brain image and brain structural statistical analysis. (Diffeomorphic anatomical registration through exponentiated Lie, DARTEL; Montreal Neurological Institute, MNI; Image calculator, ImCalc; Threshold-free cluster enhancement, TFCE)

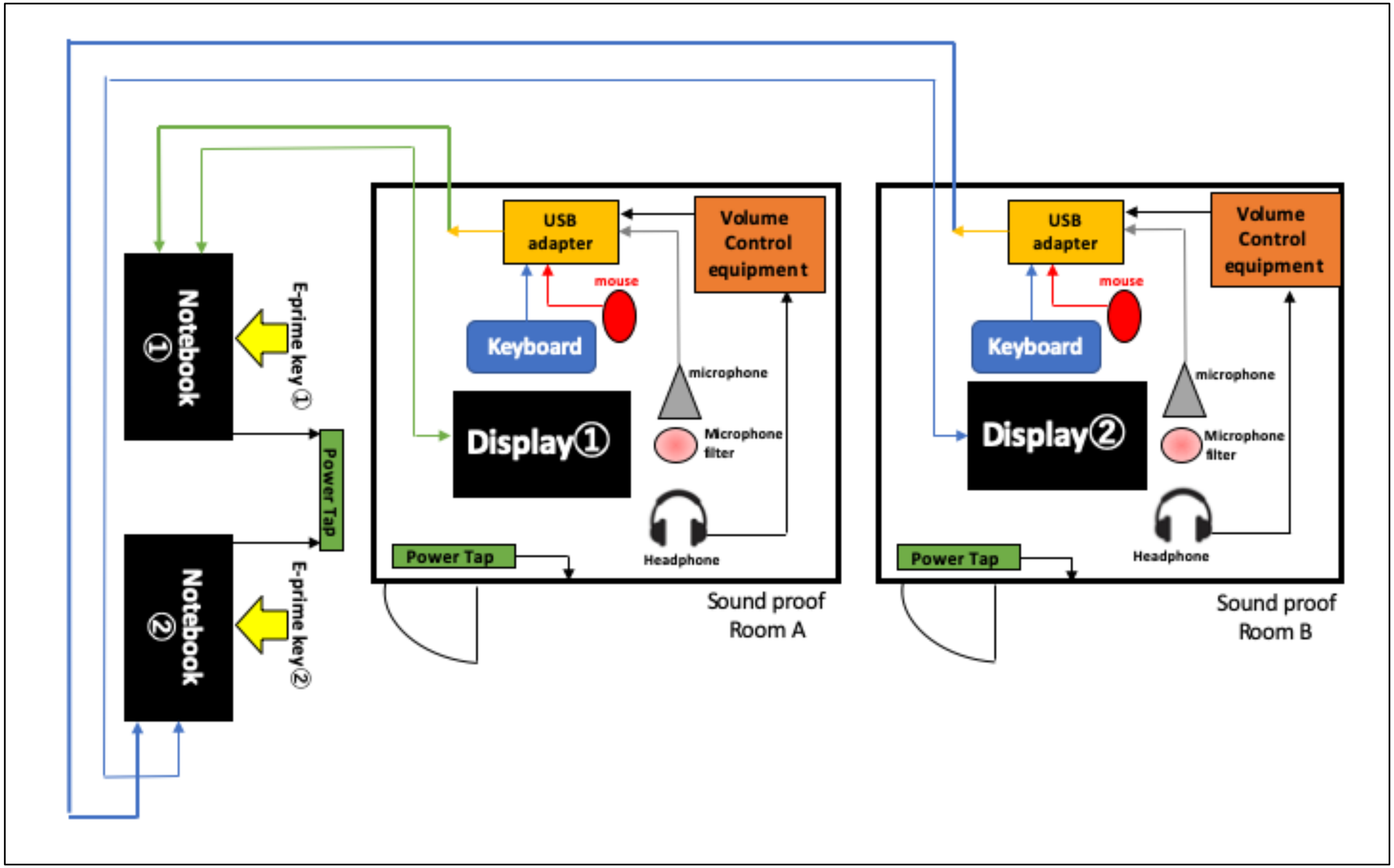
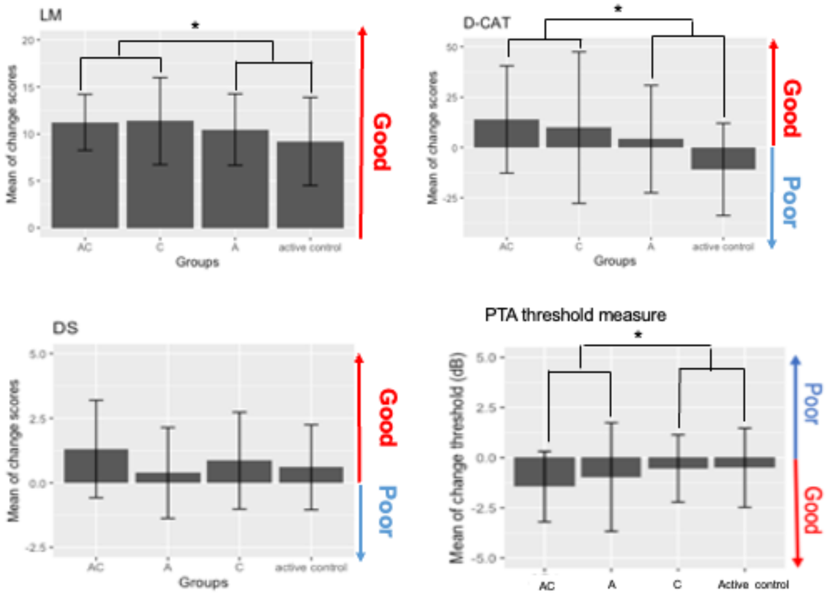


Figure 7. Training soundproof room schema setting.



*p <0.05

Figure 8. Change scores in cognitive function measures (logical memory [LM], digit cancellation [D-CAT], digit span [DS]) and auditory measures (pure-tone audiometry [PTA]) in each training group (AC, auditory-cognitive training; A, auditory training; C, cognitive training).

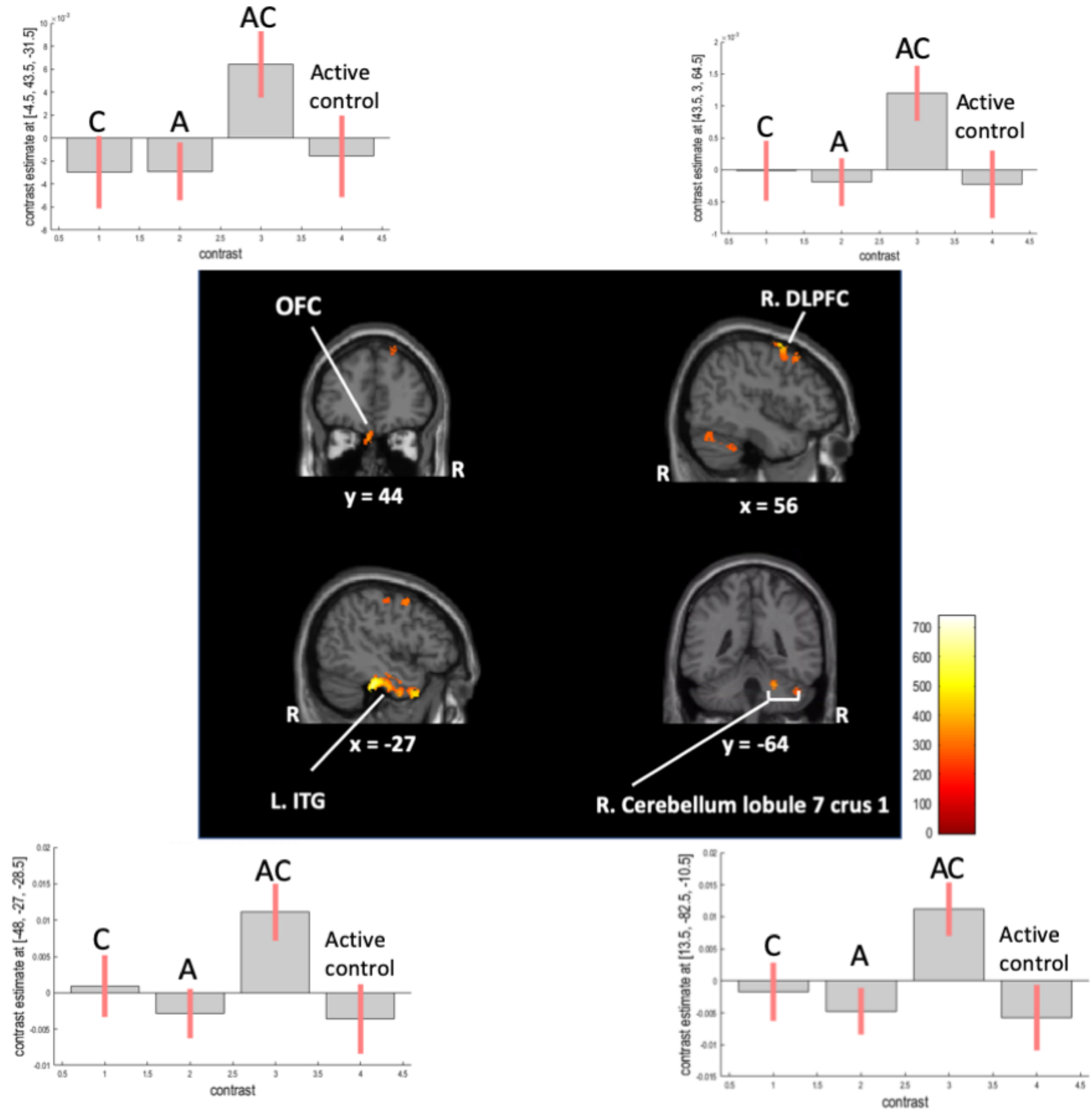


Figure 9. The regional gray matter volume results in the AC training group compared to that in the other training groups. The results shown are obtained at a threshold of the threshold-free cluster enhancement (TFCE) of $P < 0.05$ based on 5000 permutations. The color represents the strength of the TFCE value. OFC, orbitofrontal cortex; L. ITG, left inferior temporal gyrus; R. SFG, right superior frontal gyrus; AC, auditory-cognitive training; A, auditory training; C, cognitive training. FWE corrected at $p < 0.05$.

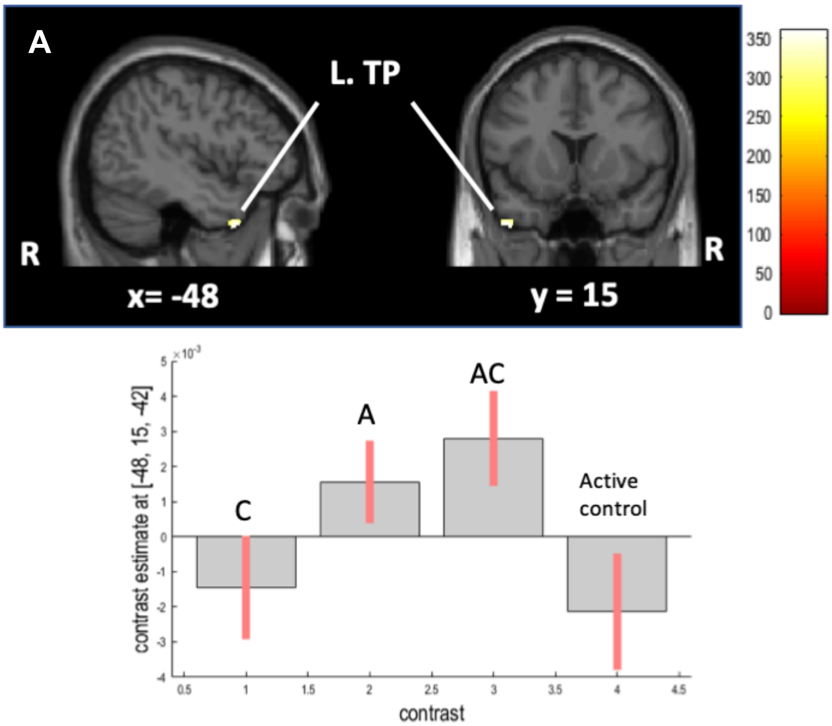


Figure 10. The regional gray matter volume results of the auditory training factor main effect (A) and cognitive training factor main effect (B). The results shown are obtained at a threshold of threshold-free cluster enhancement (TFCE) of $P < 0.05$ based on 5000 permutations. The color represents the strength of the TFCE value. L. TP, left temporal pole; AC, auditory-cognitive training; A, auditory training; C, cognitive training.

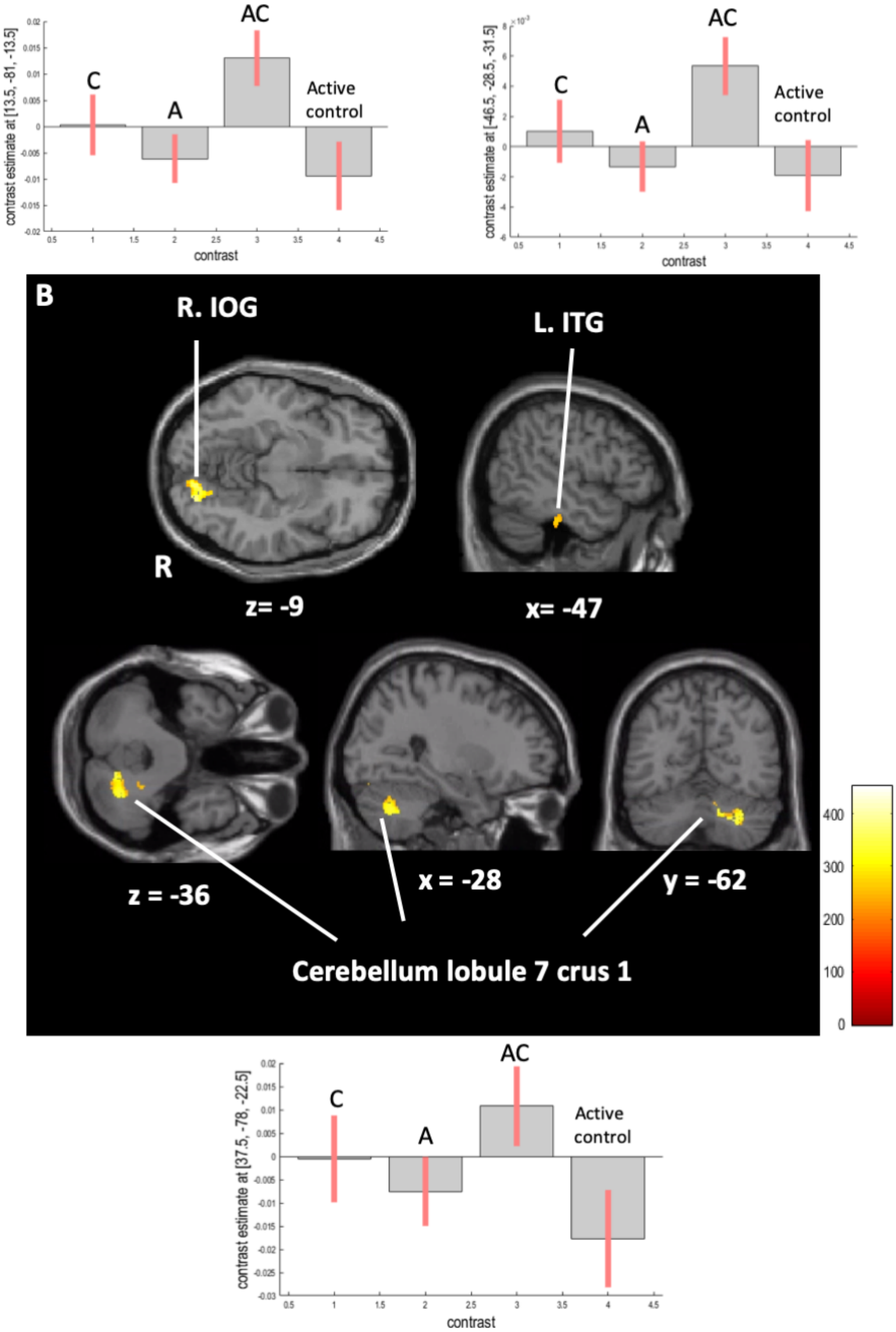


Figure 10. The regional gray matter volume results of the auditory training factor main effect (A) and cognitive training factor main effect (B). The results shown are obtained at a threshold of threshold-free cluster enhancement (TFCE) of $P < 0.05$ based on 5000 permutations. The color represents the strength of the TFCE value. R. IOG, right inferior occipital gyrus; L. ITG,

left inferior temporal gyrus; AC, auditory-cognitive training; A, auditory training; C; cognitive training.

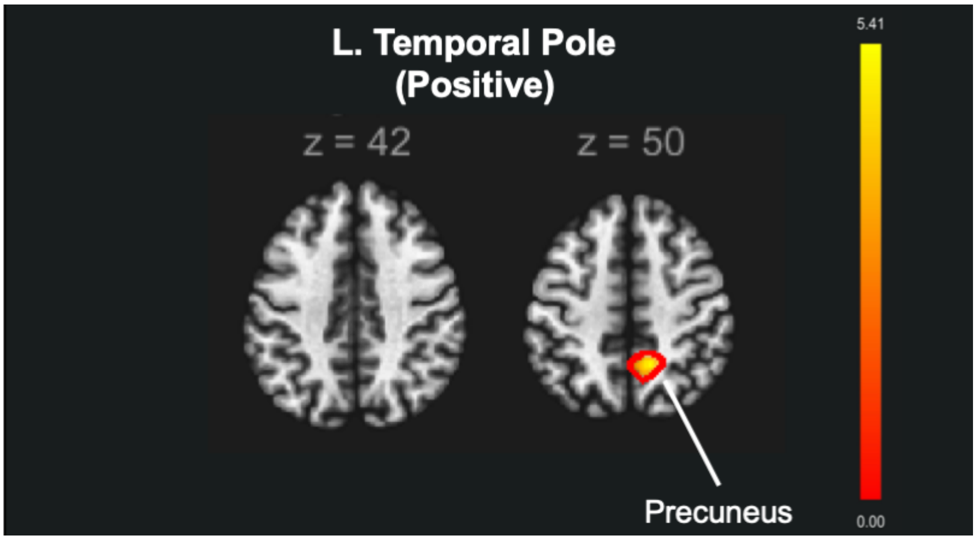


Figure 11. The functional brain connectivity of the auditory training factor groups (ATFGs) compared to the non-ATFGs. The red color represents positive functional connectivity. FWE corrected at $p < 0.05$.

Table 1. Based on the three cognitive task training (cognitive training factor) and audio stimuli volume control (auditory training factor), I set four training groups (AC training, A training, C training, and active control groups).

Training group	**Auditory training factor**	**Cognitive training factor**
AC training	+	+
A training	+	-
C training	-	+
Active control group	-	-

Table 2. List of Japanese words of the short-term memory training.

List1	List2	List3	List4	List5	List6	List7	List8	List9	List10	List11	List12
うそつき	たいよう	えいえん	けんさん	てんすう	ほんもの	いらいら	おととし	さいてい	そうめん	なきむし	ほうたい
けいさつ	たくさん	おしまい	けつろん	とくてん	まんいん	いれもの	かいせつ	さくせん	そうけい	にせもの	ほうとう
さいあく	てきとう	おちつき	けんこう	としより	むいしき	うけとり	かいてき	さくひん	たいおん	にわとり	ほんのう
しりあい	としうえ	おととい	こうえん	ないよう	めいわく	えいよう	かたまり	しおくり	たいきん	にんにく	ほうらい
せんせい	はなよめ	おわらい	こうそく	にちよう	もくてき	おうえん	かちぬき	しなもの	たいさく	ねえさん	まいあさ
たいふう	はんとし	おんせん	こくみん	にほんし	やきとり	おうふく	かつやく	しめきり	たいしつ	はきもの	まいとし
たてもの	ひこうき	かあさん	さいきん	にんしき	やくそく	おおあめ	かみきれ	しりとり	たましい	はくさい	まえむき
のみもの	ほほえみ	かいさつ	さいこう	ねんれい	やくわり	おこない	かんかく	しろくろ	ためいき	はやくち	まないた
まいにち	ほんにん	かいふく	さかみち	のうみそ	ようふく	おしいれ	かんさい	しんけい	ちんもく	はんせい	まんなか
いねむり	まよなか	かいもの	しつもん	はつこい	よふかし	おてんき	かんそう	しんせき	つきあい	はんたい	みみかき
うんめい	みそしる	かくにん	しんけん	はつめい	わりかん	おとうと	くうそう	しんせつ	つまさき	ひとこと	めのまえ
えんそく	ゆうめい	かくりつ	しんせん	ひつよう	あくにん	やすうり	けつまつ	せいかく	ていいん	ひまわり	もちもの
おはよう	らいねん	かたかな	しんゆう	ひとなみ	あしおと	やすもの	こうふく	せいけつ	てのひら	ふくすう	やきたて
こうかい	れんあい	かたみち	すなはま	ひるめし	あしもと	ゆうやけ	こうふん	せいふく	てんかい	ふみきり	やきめし
しあわせ	あやまち	かちまけ	せいせき	ふうとう	あまもり	よみかた	こくさん	せつやく	てんこう	ふるさと	あおむけ
すきやき	あんない	かみさま	せきにん	ふくそう	あらそい	らいにち	こくせき	せんぬき	とうめい	へいきん	あしあと
せいかつ	いちにち	かみのけ	せつめい	ふともも	あんしん	わかもの	こんにち	せんもん	としした	へいせい	あまくち
せんたく	うらない	かんたん	たたかい	へりくつ	いいわけ	いちねん	こんやく	そうおん	ないかく	あてさき	いきさき
たいへん	よのなか	きんにく	ちちおや	われわれ	いきぬき	いちまん	こんらん	いのしし	おかえし	かいさん	かいとう
ゆうそう	よみかき	けいけん	つうきん	いきもの	いもうと	いちまい	さいかい	いんかん	おこさま	かいてん	かおいろ

	AC-training group			**A-training group**			**C-training group**			**Active control group**			**Max Value**
	Mean	**SD**	**95% CI**	**Mean**	**SD**	**95% CI**	**Mean**	**SD**	**95% CI**	**Mean**	**SD**	**95% CI**	
Global cognitive status													
MMSE (score)	28.77	1.05	[28.10, 29.42]	29.31	0.82	[28.79, 29.82]	29.36	0.81	[28.87, 29.84]	6.8	1.6	[26.59, 29.00]	30
Working memory													
DS (score)	7.07	2.26	[5.26, 8.30]	6.69	1.97	[5.44, 7.93]	6.78	2.54	[5.64, 8.50]	5.4	1.68	[4.12, 6.67]	16
Episodic memory													
LM (score)	10.46	3.02	[8.03, 13.11]	9.53	3.41	[7.39, 11.68]	10.57	4.36	[8.55, 12.36]	8.4	4.36	[5.10, 11.69]	25
Attention													
D-CAT (score)	172.9	21.44	[148.28, 190.64]	168.6	34.98	[146.60, 190.62]	174.8	44.22	[159.43, 186.41]	164.1	44.08	[130.85, 197.340]	200
Pure-tone Audiometry													
PTA (dB)	16.44	7.58	[-2.80, 1.27]	16.54	6.28	[-2.08, 1.27]	21.43	10.71	[-2.41, 1.12]	23.88	7.86	[-2.46, 1.12]	90*

Table 3. Characteristics of participants in the AC training group, A training group, C training group, and active control group. *Maximum output limits of the audiometer. (AC, auditory-cognitive; A, auditory; C, cognitive; MMSE, Mini-Mental Examination; DS, digit span; LM, logical memory; D-CAT, digit cancellation; PTA, pure-tone audiometry threshold)

Anatomical location	Cluster size (mm^3)	Corrected p-value (FWE)	Peak MNI coordinates		
			x	y	z
AC > A + C + active control					
R. DLPFC	747	0.005	56	-5	51
L. ITG	2554	0.001	-48	-27	-29
L. SFG	682	0.025	-48	6	53
L. OFC	184	0.017	-5	44	-32
R. Cerebellum Lobule 7 Crus 1	1610	0.002	12	-87	-20
The main effect of the auditory factor					
L. TP	81	0.021	-48	15	-42
The main effect of the cognitive factor					
R. IOG	893	0.005	14	-81	-14
R. Cerebellum R. Lobule 7 Crus 1	35	0.036	38	-78	-23
ITG	71	0.032	-47	-29	-32

Table 4. Brain regional gray matter volume with a significant cluster in main effect analysis and group comparison analysis. R. DLPFC, right dorsolateral prefrontal cortex; L. ITG, left inferior temporal gyrus; L. SFG, left superior frontal gyrus; L. OFC, left orbitofrontal cortex; cerebellum lobule 7 crus 1; L. TP, the left temporal pole; R. IOG, the right inferior occipital gyrus; AC, auditory-cognitive training group; A, auditory training groups; C, cognitive training group. FWE corrected at $p < 0.05$.

Network and seed region	Brain region	Cluster size (mm^3)	p-value FWE p < 0.05	Peak MNI coordinates (X, Y, Z)			Direction of correlation
The main effect of the auditory factor							
L. TP	Precuneus	184	0.019892	+12	-52	+50	positive

Table 5. The peak MNI coordinates and intensity of brain clusters with significance in brain connectivity. L. TP, left temporal pole; AC, auditory-cognitive training group; A, auditory training group; C, cognitive training group. FWE corrected at p <0.05.

AC training group	ATFGs	CTFGs
Significant results in auditory measure		
-	PTA	-
Significant results in cognitive measures		
-	-	D-CAT
-	-	LM
Regional gay matter volume changed		
R. DLPFC	L. TP	R. IOG
L. ITG	-	Cerebellum lobule 7 Crus 1
L. SFG		
L. OFC		
R. Cerebellum lobule 7 Crus 1		
Functional connectivity increased (Seed region [Brain region])		
L. TP (Precuneus)		

Table 6. Summary of all results in the AC (auditory-cognitive) training group, the ATFGs (auditory training factor groups), and the CTFGs (cognitive training factor groups). (PTA, pure-tone audiometry; D-CAT, digit cancellation; LM, logical memory; R. DLPFC, right dorsolateral prefrontal cortex; L. TP, left temporal pole; R. IOG, right inferior occipital gyrus; L. ITG, left interior temporal gyrus; L. SFG, left superior frontal gyrus; L. OFG, left orbitofrontal cortex.

Appendix

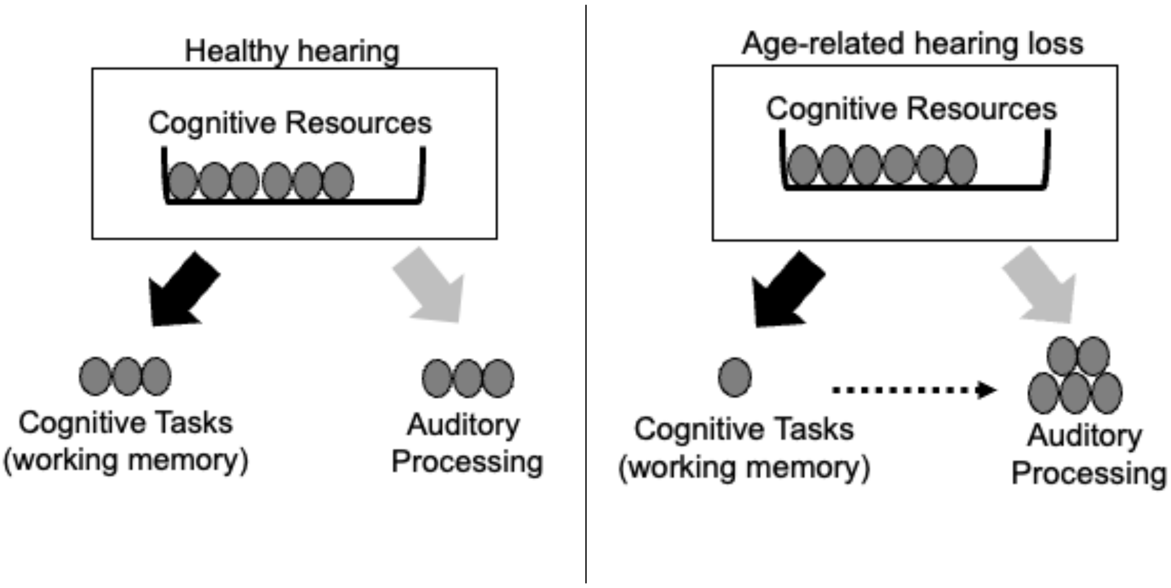


Figure. Cognitive resource in healthy hearing and age-related hearing loss. Cognitive abilities are critical under less favorable listening conditions and are sensitive to change with age. When a speech signal is poorly processed, it is transmitted from the ear to the brain, and greater cognitive resources may require to interpret the meaning of the sound than would be with a properly processed sound.

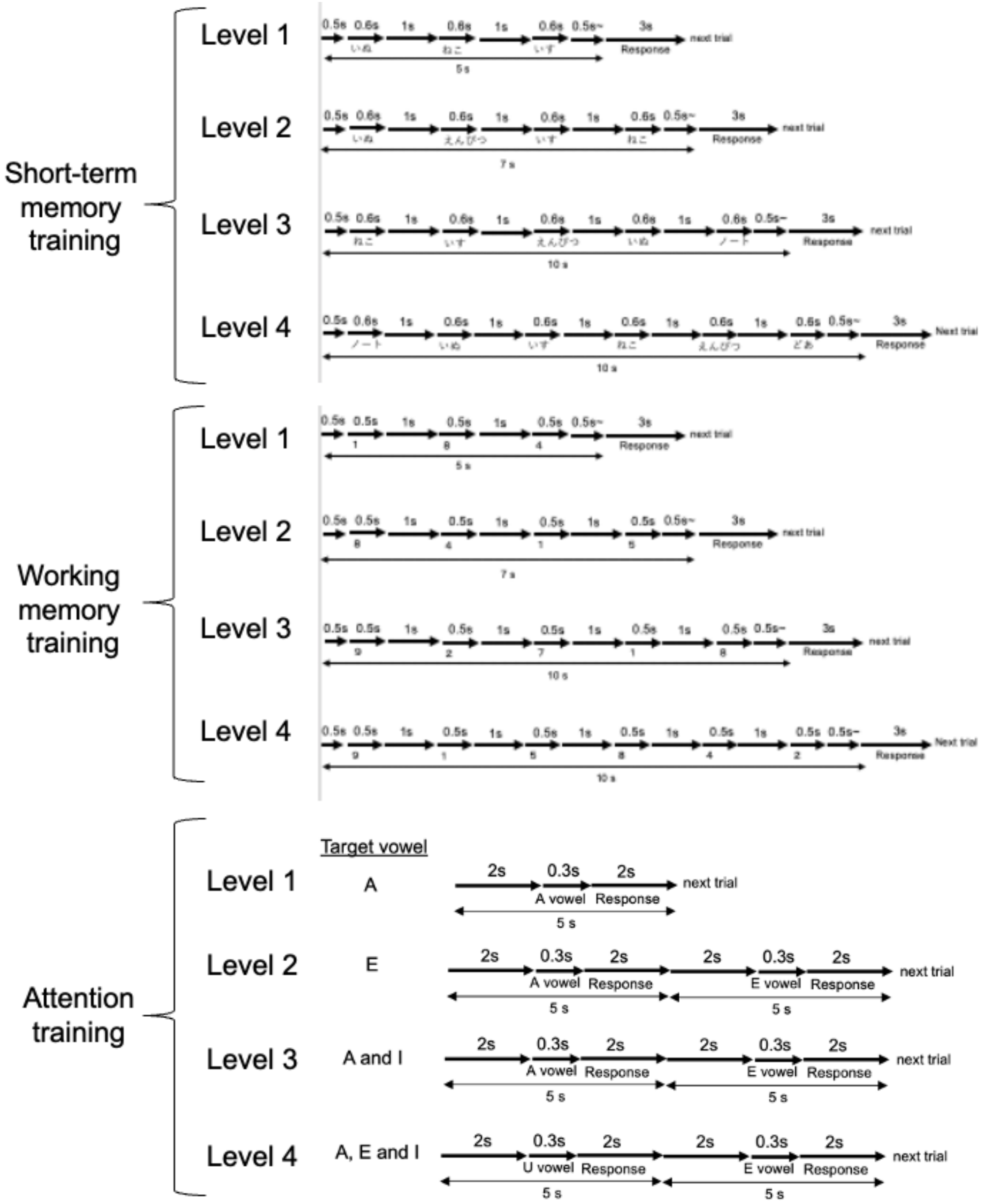
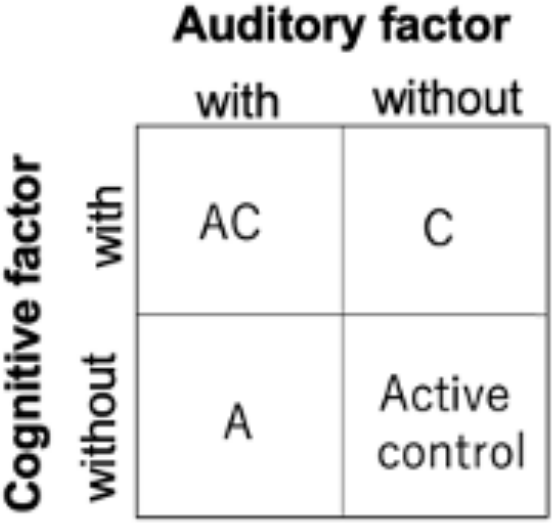


Figure. Training task schedule divided in 4 levels at each group training. Short-term memory training, working memory training, attention training.



Cognitive factor	Auditory factor: with	Auditory factor: without
with	AC	C
without	A	Active control

Figure. The two (the auditory training factor: with/without) by two (the cognitive training factor: with/without) factorial analysis covariance (ANCOVA) with permutation tests to investigate significant group differences in each cognitive measures and auditory measures. (AC, auditory-cognitive training; A, auditory training; C, cognitive training).

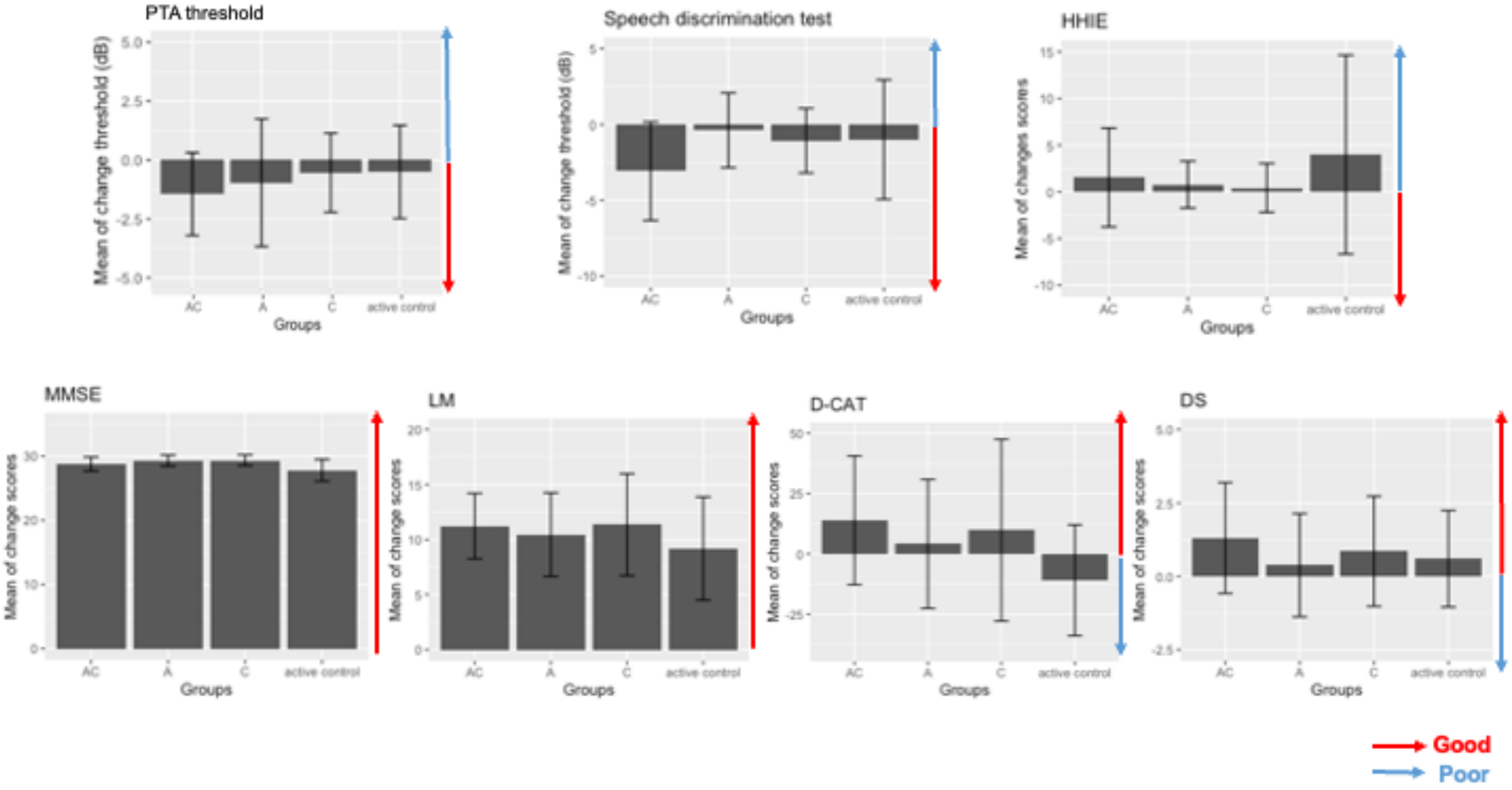


Figure. Auditory measures (PTA threshold, speech discrimination test, and HHIE) and cognitive measures (LM, D-CAT, and DS) of change scores in each training groups (AC, auditory-cognitive training; A, auditory training; C, cognitive training; active control).

Figure. Percentage of scores of each training group in 4 weeks of training.

	Training period (4weeks)							
	DAY 1	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**DAY 6**	**DAY 7**	**DAY 8**
AC training	81.80	81.80	63.40	61.60	68.80	64.40	66.40	52.80
A training	76.78	87.44	71.89	74.11	76.50	63.22	71.22	65.11
C training	71.31	82.13	67.00	71.50	63.70	72.38	59.75	58.00
Active control	78.80	96.30	97.30	97.30	97.30	98.30	98.30	98.80