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AUDITORY RADIATION AND COGNITIVE DECLINE: PROBABILISTIC
TRACTOGRAPHY STUDY

by
Adryanna Tucker

A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of
the requirements of the Sally McDonnell Barksdale Honors College.

Oxford
May 2019

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ABSTRACT

The relationship between hearing loss and Alzheimer's disease has been studied for many years. Previous studies have shown a negative correlation between the two. In our study, we investigated the relationship between the strength of the auditory radiation connections and the severity of cognitive decline. To do so, we assessed probabilistic tractography using DTI data of the primary auditory pathway. Further, we assessed the level of cognition using the Alzheimer's Disease Assessment Scale-Cog to determine the relationship between the auditory connections assessed in each patient and that patient's level of cognitive decline. We found that FA and AD were positively associated with cognitive decline.

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LIST OF ABBREVIATIONS

ADAS13	Alzheimer's Disease Assessment Scale-Cog (version 13)
AD	Axial Diffusivity
AIC/EC	Anterior Insular Cortex/Entorhinal Cortex
CC	Corpus Callosum
DSST	Digital Signal Substitution Test
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
FSL	Functional Magnetic Resonance Imaging of the Brain Software Library
MCIa	Mild cognitive impairment amnesic
MCI _{na}	Mild cognitive impairment non-amnesic
MD	Mean Diffusivity
MMSE	Mini Mental State Examination
RD	Radial Diffusivity

Introduction

Alzheimer's disease is a degenerative disease that has high prevalence worldwide. The prevalence of its death toll continues to increase, unlike other top killers which continually decrease [1]. In the United States, the disease was only responsible for 1 in 100,000 deaths in 1980 which climbed to 25 out of 100,000 deaths by 2014 [1]. A study in 2013 showed that Alzheimer's disease afflicted 13% of Americans over 65. When including those only over 85, this statistic increased to 43% [2]. Further, Alzheimer's was the fourth leading cause of death in the United States [2]. In 2017, it was reported that approximately 6.08 million Americans had either clinical Alzheimer's disease or mild cognitive impairment, a figure that is expected to grow to 15.0 million by 2060 [3]. This prevalence is also high worldwide. However, it is difficult to obtain data from all countries, especially developing regions. One study was able to estimate that in 2006, about 24.3 million people were afflicted with dementia and there was about one new case every 7 seconds [4]. Due to its large affect, many studies have researched risk factors associated with the disease. One such factor is hearing loss.

The association between hearing loss and Alzheimer's disease has been discussed for decades. In 1986, an observation study enrolled 156 Alzheimer's cases and cited hearing loss as foreshadowing cognitive dysfunction [5]. In 1989, after controlling for age, sex, and education status, they reported that hearing loss was significantly and independently linked with severity of cognitive dysfunction in an Alzheimer's case-control study [5]. A magnetic resonance brain image study indicated hearing loss

correlated with accelerated atrophy of the whole brain, especially the right temporal lobe [6]. While there are many studies that have reported an association between hearing loss and Alzheimer's disease, dementia, and cognitive dysfunction, it is still unknown what mechanisms promote this correlation and whether this correlation is causal.

However, there are many studies that show an increased risk of Alzheimer's due to hearing loss. One study shows that age related hearing loss increases a person's risk of Alzheimer's by 3.57 fold [7]. Another study found that mild hearing loss increases a person's risk of Alzheimer's by 1.9, that occupational hearing loss increases that risk by 1.7, and that severe hearing loss increases that risk by 4.9 [8]. In another study, individuals who reported moderate hearing had a 1.4 increased risk of Alzheimer's while poor hearing individuals had a 1.6 increased risk [9]. Instead of reporting the increased risk, one study reported the differences in the incidence rate of the disease. The overall incidence rate was 2.18. The incidence rate for people with bilateral hearing impairment was 3.84 while the incidence rate for unspecified hearing impairment was 2.35 [10]. A study focusing on age related hearing loss found that the regional variation in hearing impairment explained 36% of the regional variation in dementia. Further, it found the effects of age-related hearing loss on dementia to be significant in both men and women [11].

There have been hypotheses to account for the increased risks and incidence rates of Alzheimer's disease. One of the most major hypotheses is that hearing loss causes a loss of cognitive function which promotes Alzheimer's. Hearing loss is understood to cause poor cognitive function because it causes the hearing impaired to place more effort in listening, which is proven to be cognitively taxing. Further, it increases cognitive load

and thereby exhausts compensatory cognitive reallocation [12]. One study proved that greater hearing loss was significantly associated with lower scores on the Digital Signal Substitution Test after adjustment for demographic factors and medical history (DSST score difference of -1.5 [95% confidence interval: -2.9 to -0.23] per 10 dB of hearing loss) [13]. Further, when use of a hearing aid was added, there was a positive association with cognitive functioning (DSST score difference of 7.4 [95% confidence interval: -0.62 to 15.4]) [13]. With a decrease in cognitive function, Alzheimer's is more likely to appear.

Further, there are other possible accounts. It has been hypothesized that the brain structure and function is changed due to hearing loss and increases the risk of Alzheimer's [8]. There is a correlation between hearing loss and loss of brain volume. These changes may account for Alzheimer's incidence. Other researchers suggest that the effects of hearing loss on an individual's life increase the risk of Alzheimer's. For example, hearing loss may cause social isolation in the elderly. Since there is a relationship between poor social communication and dementia, this is also a possible explanation [11]. The relationship between hearing loss and Alzheimer's disease remains unclear.

Memory, specifically, has been found to be influenced by hearing loss. Though there is little research on this relationship, one study of mice revealed that induced hearing loss was associated with memory decline [14]. In the study, following a noise exposure, which created moderate to severe hearing loss, a deficit in spatial and learning memory was seen [14]. This deficit was correlated with the degree of hearing loss and associated with a decrease of neurogenesis in the hippocampus [14].

Diffusion Tensor Imaging (DTI) is a technique used to examine the integration of axonal white matter in the brain. This technique allows examining of the auditory radiation, the transmission from the medial genicular nucleus to the primary auditory cortex which is the final part of the pathway from the cochlea to the cerebral cortex. This final transmission completes the auditory pathway in order to successfully perceive sound. Although the auditory radiation can be assessed by probabilistic tractography using DTI data, it is not clear whether the auditory radiation is influenced in Alzheimer's disease. In this study we examined the auditory radiation in Alzheimer's disease, using probabilistic tractography on DTI data. Specifically, we tested the association between the integrity of the auditory radiation and cognitive decline assessed by Alzheimer's Disease Assessment Scale-Cog (ADAS-Cog).

Methods

DTI data were obtained from ADNI, along with demographic and Pittsburgh Sleep Quality. Samples from 288 individuals (72.52 ± 7.10 , 130 females and 155 males) contained DTI and ADAS13 data. The analyses in this study were approved by the Institutional Review Board of the University of Mississippi (14x-244). ADAS13 questions are listed in appendix 1.

The DTI series had 41 volumes of noncolinear directions as well as 5 volumes without diffusion weighting ($TR = 7200\text{ms}$, $TE = 56\text{ms}$, matrix = $232 \times 232 \times 160$) with 2mm^3 isotropic resolution.

Image processing was conducted using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL version 5.1; Oxford, United Kingdom; <http://fsl.fmrib.ox.ac.uk/fsl>). Eddy-current induced distortions and head-motion displacements were corrected through affine registration of the 31 diffusion volumes to the first b_0 volume using FSL's Linear Registration Tool. The b-vector table (i.e., gradient directions) for each participant was then adjusted according to the rotation parameters of this linear correction. Non-brain tissue was removed using FSL's Brain Extraction Tool. Fractional anisotropy (FA), an index of white matter integrity, was then calculated at each voxel of the brain by fitting a diffusion tensor model to the raw diffusion data using weighted least squares in FSL's Diffusion Toolbox.

The local (i.e., within-voxel) probability density functions of the principal diffusion direction were estimated using Markov Chain Monte Carlo sampling in FSL's

Bedpostx tool [15]. A spatial probability density function across voxels was then estimated based on these local probability density functions using FSL's Probtrackx tool [15], in which 5000 samples were taken for each input voxel with a 0.2 curvature threshold, 0.5 mm step length, and 2000 steps per sample. Segmentation of the auditory radiation tracts and termination masks was determined based on the MNI152 T1 brain provided in FSL, using FSL's FMRIB58_FA template as a DTI specific reference. MGN seed was defined as a R=3mm sphere centered at MNI: $\pm 18, -26, -6$.

The primary auditory cortex seed was determined by taking the adjacent white matter region to the Heschl's gyrus in the HarvardOxford cortical atlas (15). The termination masks excluding contralateral projections were defined MNI $x < -15$ (left) and $x > +15$ (right). The bilateral auditory radiation of each subject was then thresholded at a normalized probability value of 0.05. The mean FA within the bilateral auditory radiation was calculated for each individual.

To assess the association between the auditory radiation FA and cognitive decline, a multiple linear regression was calculated to predict the auditory radiation FA based on the ADAS13 score and age.

As secondary measures, Axial Diffusivity (AD), Radial Diffusivity (RD) and Mean Diffusivity (MD) were also tested. A multiple linear regression was calculated to predict the auditory radiation AD/RD/MD based on the ADAS13 score, age and sex.

Results

Probabilistic tractography successfully isolated the auditory radiations. In visual inspection, the auditory radiation of each individual subject conformed to the known white matter structure of the auditory radiations (Figure 1).

The mean ADAS13 score was 15.535 ± 8.88 . In the statistical test, a significant regression equation was found ($F(2,282)=3.03$, $p=0.0497$), with an R^2 of 0.014. The predicted auditory radiation FA is equal to $0.43 + 0.00058 (\text{ADAS13}) - 0.00038 (\text{age})$. ADAS13 ($p=0.021$) significantly predicted the auditory radiation FA (Figure 2).

AD but not RD or MD predicted ADAS13. Significant regression was found in AD, RD, and MD. ADAS significantly predicted AD but not AD and MD. The predicted auditory radiation AD ($F(2,282)=28.26$, $p<6.50e-12$), with an R^2 of 0.099 where the predicted auditory radiation AD is equal to $0.00095 + 0.0000013 (\text{ADAS13}, p=0.00055) + 0.0000028 (\text{age}, p=5.82e-09)$. The predicted auditory radiation RD ($F(2,282)=8.30$, $p=0.00031$), with an R^2 of 0.049 where the predicted auditory radiation RD is equal to $0.00047 + 7.682e-8 (\text{ADAS13}, p=0.84) + 1.88e-6 (\text{age}, p=0.000087)$. The predicted auditory radiation MD ($F(2,282)=16.57$, $p=1.5712e-7$), with an R^2 of 0.099 where the predicted auditory radiation MD is equal to $0.0000063 + 4.8e-7 (\text{ADAS13}, p=0.15) + 2.178e-6 (\text{age}, p=2.86e-7)$.

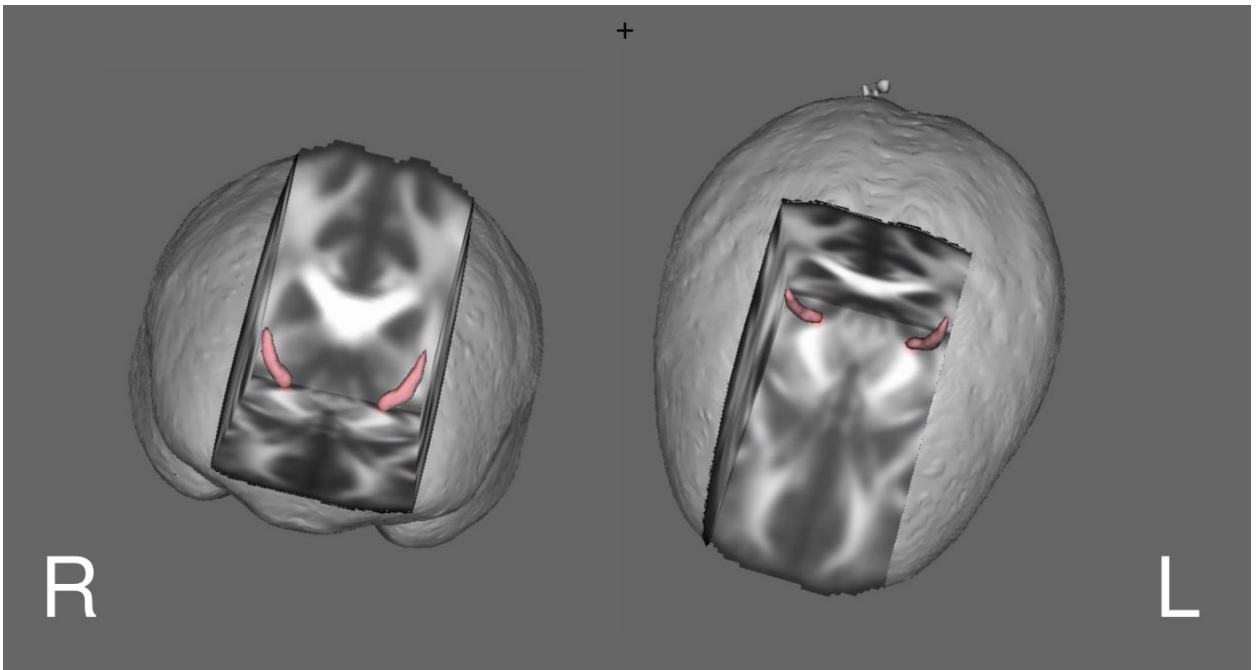


Fig 1. Probabilistic Tractography of the Auditory Radiation

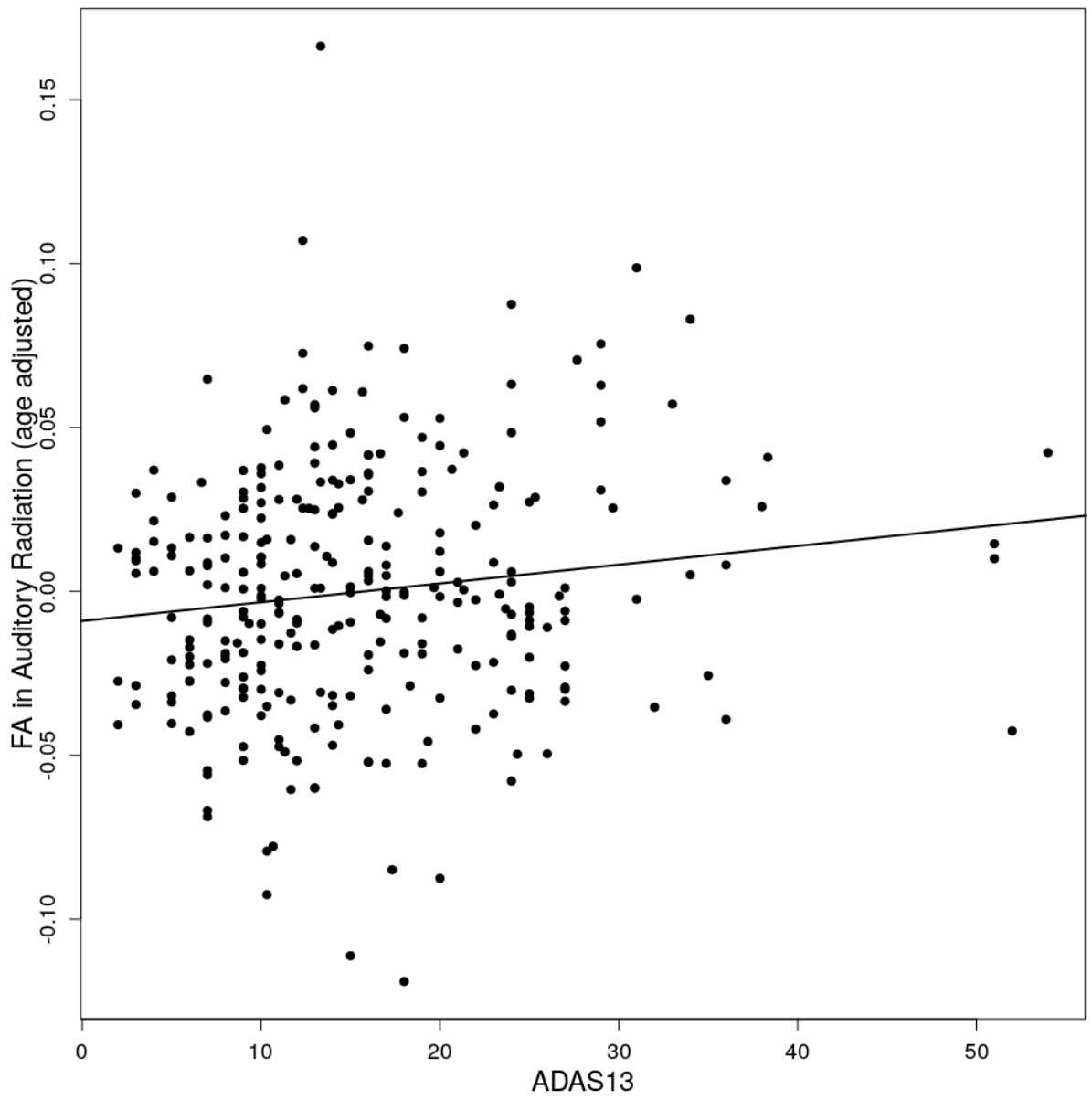


Fig 2. Association between ADAS13 and Auditory Radiation FA

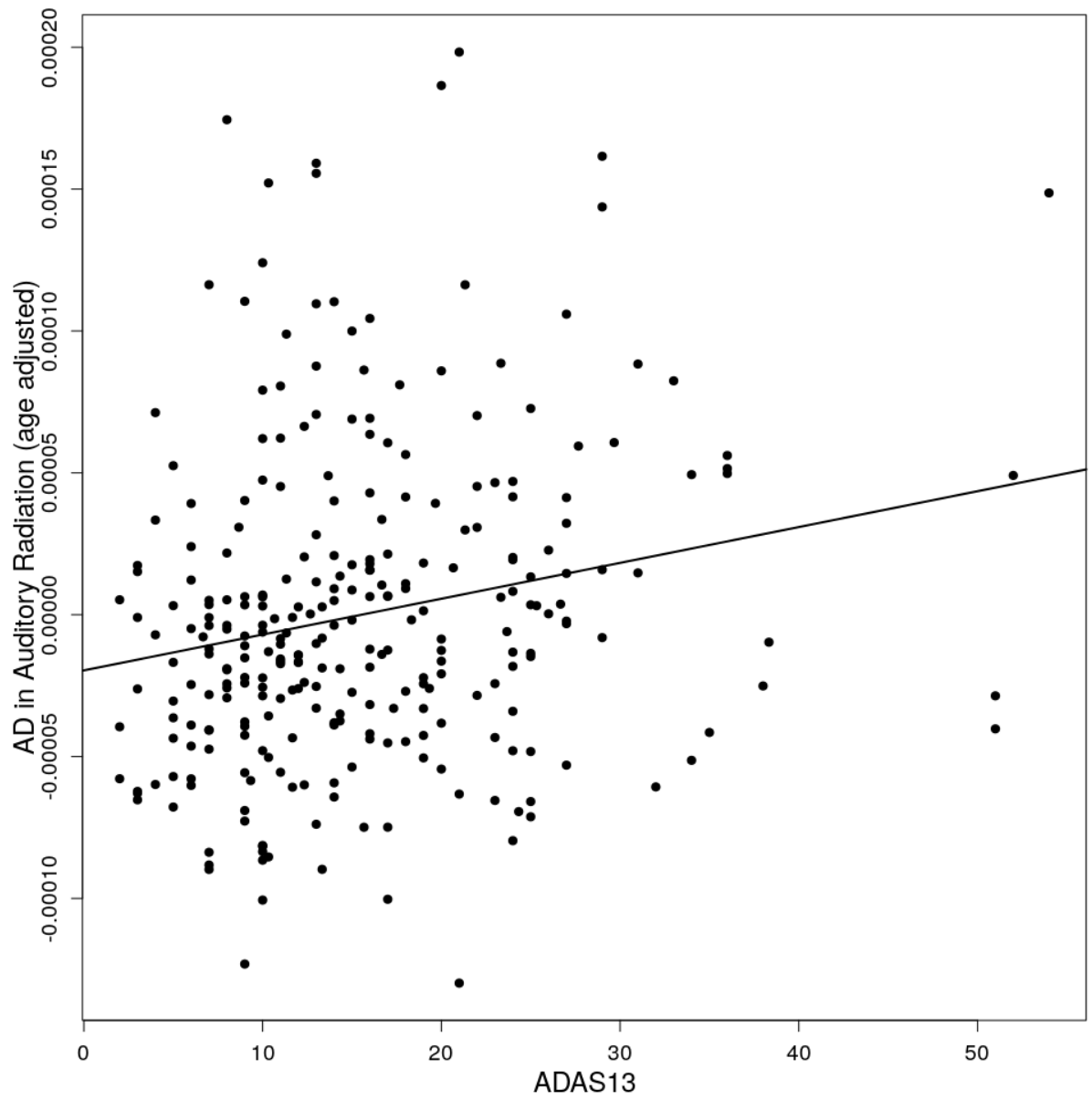


Fig 3. Association between ADAS13 and Auditory Radiation AD

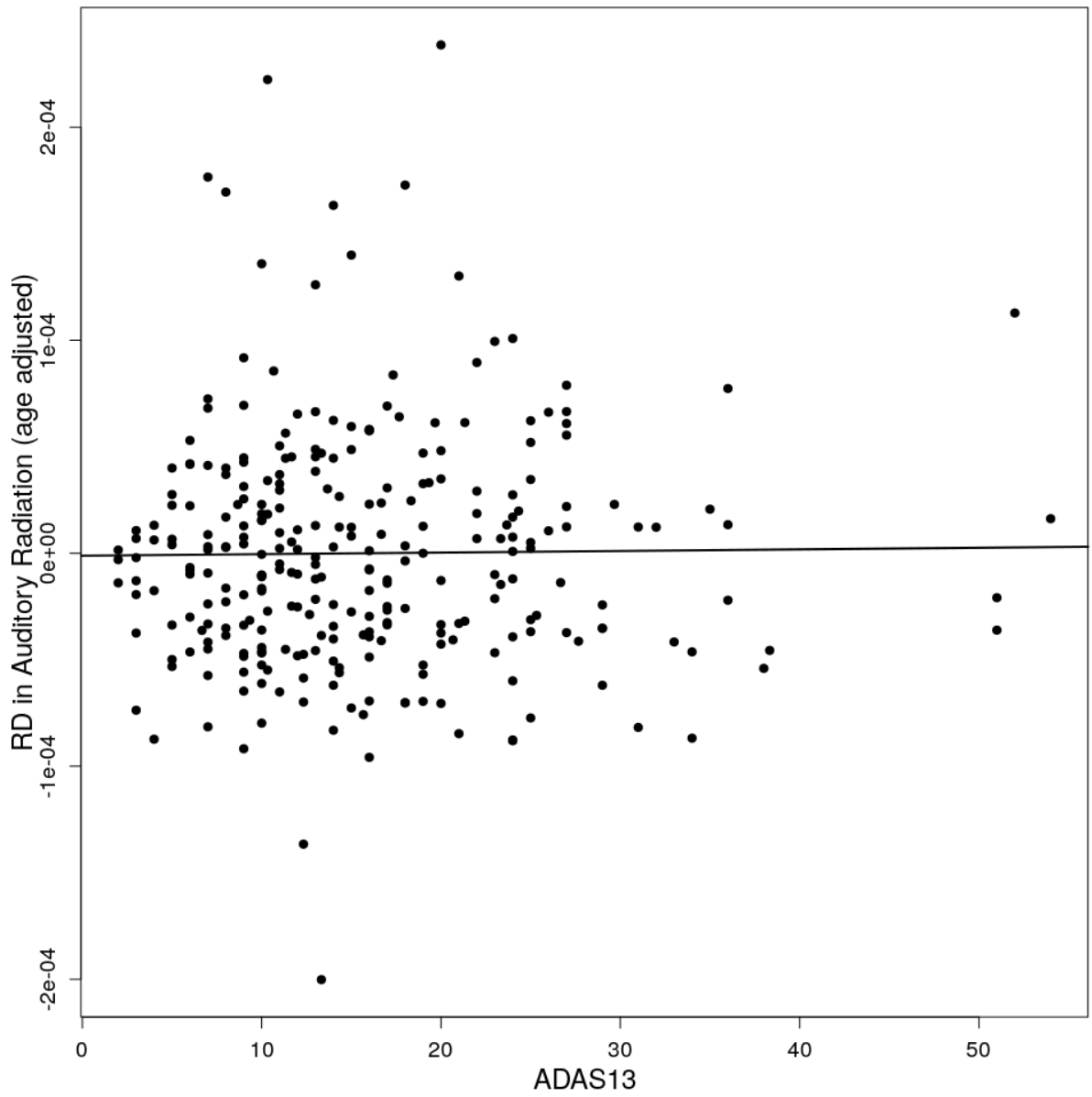


Fig 4. Association between ADAS13 and Auditory Radiation RD (not significant)

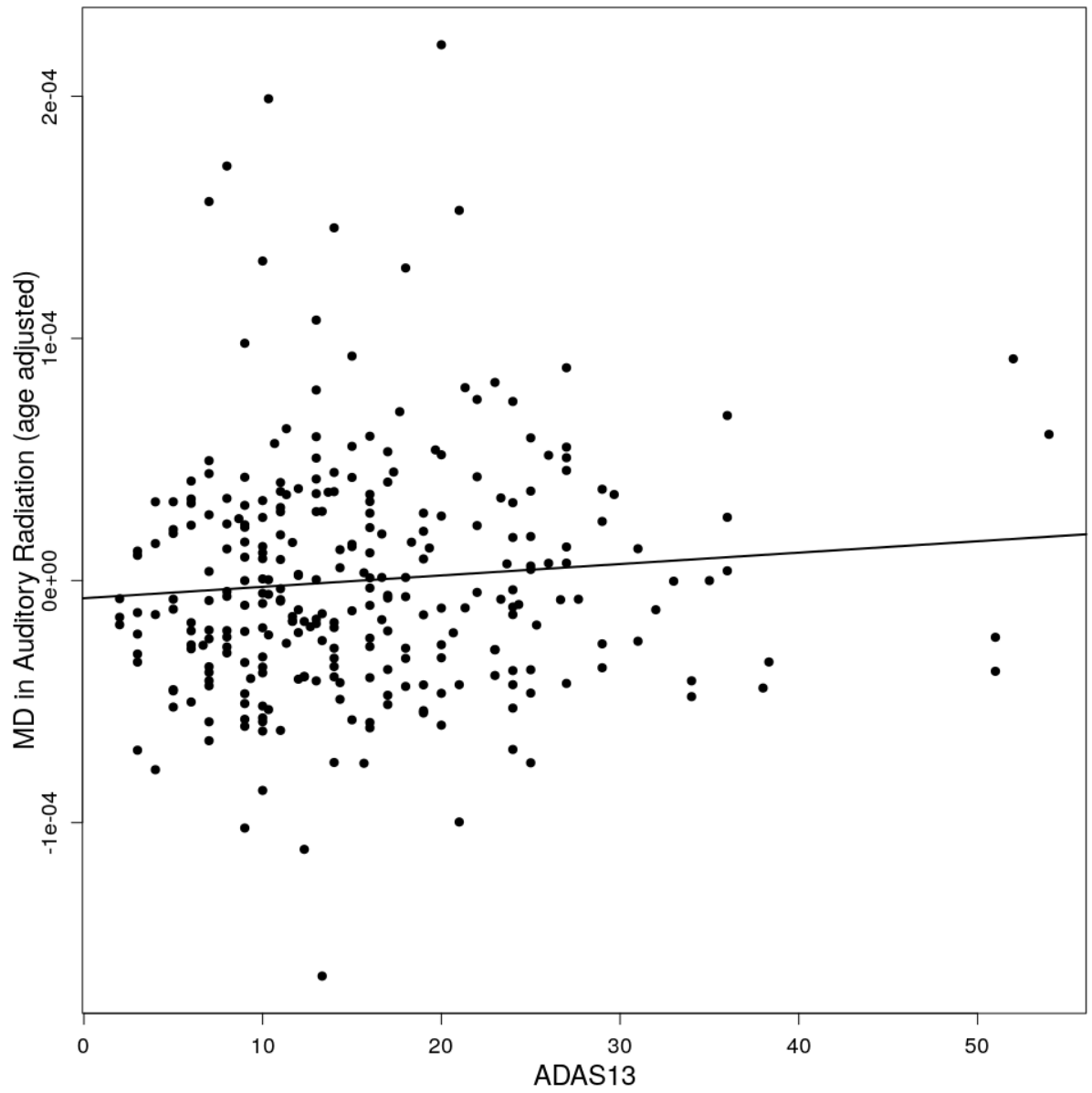


Fig 5. Association between ADAS13 and Auditory Radiation MD (not significant)

Discussion

In this study, we tested the association between the integrity of the auditory radiation and cognitive decline. The FA of the auditory radiation showed positive association with ADAS 13 score, indicating higher white matter integrity of the auditory radiation in those who with more cognitive decline.

As evaluations to FA (fractional anisotropy), axial, radial and mean diffusivities were examined in their associations to ADAS 13. AD showed significant association with ADAS13. It is suggested that the association between FA and ADAS13 is driven by association between FA and ADAS13. FA is calculated in the following way, in which lamda1 stands for AD, lambda 2+3 for RD, lambda 1+2+3 for MD.

$$FA = \frac{\sqrt{3(\lambda_1 - E[\lambda])^2 + (\lambda_2 - E[\lambda])^2 + (\lambda_3 - E[\lambda])^2}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}} \quad (1)$$

AD corresponds to axonal integrity. For example, reduced axial diffusivity is thought to reflect axonal degeneration [16], especially in white matter regions of high fiber coherence. Therefore, a high AD shows higher axonal integrity. Alzheimer's patients had a higher AD as the severity of their Alzheimer's increased which shows that as the severity increases, the higher the connectivity of the auditory pathway.

Many studies reported increased AD in Alzheimer's disease and early cognitive impairment. One study shows that axial diffusion was increased in multiple white matter structures, including the corpus callosum and the white matter of lateral temporal cortex, the posterior cingulate cortex/precuneus and the fronto-parietal regions [17]. In another study, patients with amnesic mild cognitive impairment (MCIa) had significantly higher AD in the left frontal regions of the brain, including the forceps minor and parts of the left prefrontal cortex, when compared to the control [18]. Further, their study also investigated non amnesic mild cognitive impairment (MCI_{na}) and when compared to MCIa, MCIa had significantly higher AD in the left dorsal and ventral prefrontal cortex, including the forceps minor and uncinate fasciculus. Another study investigated the AD in both normal aging and in Alzheimer's and found that AD in Alzheimer's patients was higher in all six fibers except fiber bundles from the genu of the CC; whereas the normal old group had higher DA only in the right AIC/EC and right splenium [19]. The basis for these findings is unknown. However, in a study of diffusion tensor metrics, it was found that progressive abnormalities in the FA and RD were only seen in areas that first had an increase in AD and MD [20]. Therefore, they hypothesized that increased AD represents an upstream event that precedes neuronal loss.

In our study, we found that AD in the auditory radiation is associated with cognitive decline, assessed by ADAS13. In the study seen in [17], the criteria used to show the cognitive decline of Alzheimer's patients was the Mini Mental State Examination (MMSE). In [18], participants' cognition was assessed using MMSE as well. The study in [19] also used MMSE to determine the level of cognition of all participants volunteering in the study. In the study seen in [20], participants' cognition

was assessed with both MMSE and Addenbrooke's cognitive examination-revised score out of 100-point total (ACE-R/100). In all of the studies mentioned, the cognitive scores for participants with Alzheimer's or MCI showed cognitive decline, but patients with Alzheimer's showed greater cognitive decline.

We have expected that the white matter integrity measured by FA is inversely associated with cognitive decline. However, our results indicated positive associations with them. This is surprising due to many studies that show cognition and hearing are positively correlated. Specifically, in one study, it was seen that all domains of cognition were significantly poorer in individuals with untreated hearing loss and remained poorer in individuals with treated hearing loss when compared to individuals with normal hearing [21]. Therefore, our results that showed stronger connections, via increased AD and FA, in the auditory pathway is surprising and it is unknown why these parameters increased rather than decreasing, as was predicted. However, these results were seen in multiple other studies.

Limitation of this study includes that we have no information about the status of hearing in these participants. In our interpretation of the results, we assumed that the higher FA in the auditory radiations refers to better hearing. However, we have no confirmatory data to support this. Further, we have no information about the participants' hearing parameters before the onset of their cognitive decline and are therefore unable to determine if hearing differences caused Alzheimer's disease or if Alzheimer's disease caused the hearing differences seen.

In conclusion, we found that FA and AD of the auditory radiations are positively associated with cognitive decline. When using ADAS13 to test for cognition, it was seen

that the higher the cognitive decline, the higher the FA and AD of the auditory radiation. Higher FA and AD correspond to a stronger connection in the primary auditory radiation and therefore are associated with increased hearing ability. This is surprising due to previous studies that suggest that higher cognitive decline is associated with increased hearing loss. Therefore, due to our limitations, in order to understand these results and determine the true relationship between hearing and cognitive ability, more studies should be performed.

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APPENDIX

Alzheimer's Disease Cooperative Study

ADAS – Cognitive Behavior

1. WORD RECALL TASK: Indicate the total number of correct responses for each trial

Trial 1: Trial 2: Trial 3:

2. NAMING OBJECTS AND FINGERS: Check each object/finger named correctly or check "NONE."

NONE Flower Rattle Wallet Bed Mask Harmonica
Whistle Scissors Stethoscope Pencil Comb Tongs
Thumb Index Ring Pinky Middle

3. COMMANDS: Check each command performed correctly or check "NONE."

NONE

Make a fist.

Point to the ceiling, then to the floor.

Put the pencil on top of the card, then put it back.

Put the watch on the other side of the pencil and turn over the card.

Tap each shoulder twice with two fingers keeping your eyes shut.

4. CONSTRUCTIONAL PRAXIS: Check each figure drawn correctly.

None: attempted but drew no forms correctly.

Patient drew no forms; scribbled; wrote words.

Circle

Two overlapping rectangles

Rhombus

Cube

5. IDEATIONAL PRAXIS: Check each step completed correctly or check "NONE"

- NONE
- Fold a letter.
- Put letter in envelope.
- Seal envelope.
- Address envelope.
- Indicate where stamp goes.

6. ORIENTATION: Check each item answered correctly or check "NONE."

- NONE
- Full name Day
- Month Season
- Date Place
- Year Time of day

7. WORD RECOGNITION TASK: Scoring will be done by the A.D.C.S. Data Coordinating Center.

8. LANGUAGE: Check level of impairment.

- None: patient speaks clearly and/or is understandable.
- Very Mild: one instance of lack of understandability.
- Mild: patient has difficulty < 25% of the time.
- Moderate: patient has difficulty 25–50% of the time.
- Moderately Severe: patient has difficulty more than 50% of the time.
- Severe: one- or two-word utterances; fluent, but empty speech; mute.

9. COMPREHENSION OF SPOKEN LANGUAGE: Check level of impairment

- None: patient understands.
- Very Mild: one instance of misunderstanding.
- Mild: 3–5 instances of misunderstanding.

Moderate: requires several repetitions and rephrasing.

Moderately Severe: patient only occasionally responds correctly; i.e., yes – no questions.

Severe: patient rarely responds to questions appropriately; not due to poverty of speech.

10. WORD FINDING DIFFICULTY: Check one response.

None.

Very Mild: 1 or 2 instances, not clinically significant.

Mild: noticeable circumlocution or synonym substitution.

Moderate: loss of words without compensation on occasion.

Moderately Severe: frequent loss of words without compensation.

Severe: nearly total loss of content words; speech sounds empty; 1– to 2-word utterances.

11. REMEMBERING TEST INSTRUCTIONS: Check level of impairment.

None.

Very Mild: forgets once.

Mild: must be reminded 2 times.

Moderate: must be reminded 3–4 times.

Moderately Severe: must be reminded 5–6 times

Severe: must be reminded 7 or more times.

Present Word List #2.

Check EACH word correctly recalled.

TRIAL 1		TRIAL 2		TRIAL 3	
BOTTLE	<input type="checkbox"/>	FOREST	<input type="checkbox"/>	GIRL	<input type="checkbox"/>
POTATO	<input type="checkbox"/>	TEMPLE	<input type="checkbox"/>	TEMPLE	<input type="checkbox"/>
GIRL	<input type="checkbox"/>	BOTTLE	<input type="checkbox"/>	POTATO	<input type="checkbox"/>
TEMPLE	<input type="checkbox"/>	STAR	<input type="checkbox"/>	ANIMAL	<input type="checkbox"/>
STAR	<input type="checkbox"/>	POTATO	<input type="checkbox"/>	FOREST	<input type="checkbox"/>

ANIMAL	<input type="checkbox"/>	GIRL	<input type="checkbox"/>	LAKE	<input type="checkbox"/>
FOREST	<input type="checkbox"/>	CLOCK	<input type="checkbox"/>	OFFICE	<input type="checkbox"/>
LAKE	<input type="checkbox"/>	ANIMAL	<input type="checkbox"/>	CLOCK	<input type="checkbox"/>
CLOCK	<input type="checkbox"/>	LAKE	<input type="checkbox"/>	BOTTLE	<input type="checkbox"/>
OFFICE	<input type="checkbox"/>	OFFICE	<input type="checkbox"/>	STAR	<input type="checkbox"/>

Indicate total number of words correctly recalled for EACH trial on the ADAS Cognitive Behavior Form below.

Trial 1: Trial 2: Trial 3:

12. Executive Function (Maze):

a. number of errors:

b. time at completion or second error (total seconds):

13. Number Cancellation:

a. number of targets hit (Range: 0 - 40):

b. number of errors:

c. number of times to remind of task:

If any item(s) 1-13 are incomplete or not done, please specify reason:

Subject too cognitively impaired to complete

Subject was unable to complete for physical reasons

Subject refused

Not Done, for reason other than above explain:

Alzheimer's Disease Cooperative Study

ADAS – Delayed Recall

Instructions: Say to the patient, “NOW I WANT YOU TO TRY TO REMEMBER THE WORDS THAT I SHOWED YOU EARLIER ON PRINTED CARDS. CAN YOU TELL ME ANY OF THOSE WORDS?”

Allow a maximum of two minutes for recall.

check EACH word correctly recalled.

BOTTLE

POTATO

GIRL

TEMPLE

STAR

ANIMAL

FOREST

LAKE

CLOCK

OFFICE

TOTAL:

Alzheimer's Disease Cooperative Study

ADAS – Word Recognition

Present Word List #2.

Check subject's response for each word. Subject should respond "yes" to original words which are bolded. Three trials of reading and recognition are given.

Answer	Answer	Answer
COST	BATTLE	VISITOR
NATION	MUCH	ACID
CHIMNEY	TUBE	SPEAK
SPARROW	TEAM	SOLUTION
DAMAGES	COPY	NAME
TRAFFIC	ENGINE	MEAL
SANDWICH	GRAVITY	LINE
SERVICE	COST	BILL
SHELL	JAR	CHIMNEY
SOLUTION	DISTANCE	ENGINE
YARD	TRIUMPH	WEALTH
TUBE	TEMPER	TUBE
BODY	SENTENCE	IMAGE
GROUND	FOX	COST
STICK	PASSENGER	SANDWICH
ENGINE	SANDWICH	DAMAGES
RICHES	SOLUTION	ELEPHANT
GRAVITY	WHISTLE	RICHES
SUMMER	CHIMNEY	GRAVITY
WISDOM	UNION	FUTURE
MAN	ACID	PASSENGER
MEAL	MEAL	STRING
PASSENGER	DAMAGES	BANNER
ACID	RICHES	BERRY

Correct responses:

