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Preventing Alzheimer's: Effects of Second Language Acquisition in Older Populations

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Honors Thesis

PREVENTING ALZHEIMER'S: EFFECTS OF SECOND LANGAUGE ACQUISITION IN OLDER POPULATIONS

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ABSTRACT

PREVENTING ALZHEIMER'S: EFFECTS OF SECOND LANGAUGE ACQUISITION IN OLDER POPULATIONS

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Alzheimer's disease continues to be a problem that medicine has few answers for. As a result, much research has been focused on finding a cure as well as interventions to help prevent the onset of the disease. One such intervention that has been proposed is to improve the brain's efficiency and connectivity. A controversial method of achieving these results is through second language acquisition. Many provide evidence for or against the benefits of this intervention, but much remains unclear. Most of these studies focus on cognitive function and functional connectivity in language areas, but the default mode network, which is known to align with the earliest regions affected by Alzheimer's disease, has been largely unexplored. This paper analyzes the changes in memory performance and functional connectivity of the default mode network in middle to older aged subjects who participated in a three month long Spanish course. There were no significant changes in memory and the results suggest that the changes in functional connectivity caused by the language course were not related to memory. Changes in functional connectivity were found to be significant in three of nine regions of interest (ROIs) in the default mode network including the posterior cingulate cortex (PCC) and

inferior parietal lobes, which were identified by Greicius et al. (2004) as being areas affected early on in the onset of Alzheimer's disease. These findings provide additional evidence that second language learning at an advanced age does improve functional connectivity and help prevent Alzheimer's disease.

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Introduction

Alzheimer's disease has grown to be the sixth leading cause of death in the United States and is now third as a cause of death for people at an advanced age (*Alzheimer's Disease Fact Sheet,* 2019). Without a cure and being irreversible, Alzheimer's leads to a gradual decline in memory and thinking skills until those affected by it are left without the ability to complete the simplest of tasks. Evidence has shown that the changes in the brain that define Alzheimer's can precede these symptoms by more than ten years, and these symptoms develop later when the brain goes under a process of severe shrinking. Due to its drastic consequences and high prevalence, Alzheimer's disease has been marked as a research area of high importance within the global research community.

A key focus of research has been about how to both prevent and delay the onset of Alzheimer's. Specific topics of interest include genetic and acquired risk factors, as well as protective factors, such as physical activity, diet, hormone replacement therapy, and cognitive reserve (Silva et al., 2019). For this paper, the most relevant factor is cognitive reserve, which is a theory that focuses on the observed discrepancy between the degree of brain damage in certain patients and the severity of their cognitive decline (Xu et al., 2015). It has been proposed that some patients have a greater cognitive reserve, either through greater available neural substrate or greater efficiency and connectivity in areas like the default mode network, that allows them to better function in the presence of brain damage. An important area of research with the potential of preventing Alzheimer's disease and increasing this cognitive reserve is the benefits of second language acquisition.

Bilingualism has been a topic of research for many years and has undergone many significant changes with respect to the overall perspective of the scientific community on its effects. Up until the middle of the twentieth century, it was thought that being bilingual was harmful to health and to society, causing retardation and stunting growth, but the past few decades have brought a surge of new research with the advent of new techniques and ways to image the brain that have triumphed the cognitive benefits of bilingualism (Saer, 1923; Vince, 2016). For years, there was an unquestioned consensus that bilingualism had significant cognitive benefits, but, in recent years, these findings have come under great scrutiny.

Researchers began to attempt to replicate the results that supported the increase in cognitive function but were unable to do so (Vince, 2016). Soon the research community was flooded with studies that both supported and denied the supposed benefits of bilingualism. Others such as Blanco-Elorrieta and Pylkkänen (2018) called for a redefinition of what aspects of bilingualism were causing these benefits and the extent to which they are happening. As of now, the research has yet to come to a conclusive decision on the effects of bilingualism.

This research hopes to contribute data to a more specific subset of bilingualism which is the acquisition of a second language at an advanced age. Most of the current research on bilingualism points toward the benefits only being for those who acquired the language in childhood (Williams, 2015). That being said, much like the general literature on bilingualism, there is great controversy about the benefits of a later age of acquisition. Klimova et al. (2020) found a lack of cognitive enhancement in a study involving second language acquisition with elderly participants while Bubbico et al. (2020) showed improved global cognitive functions and increased functional connectivity in language areas such as the inferior frontal gyrus and right superior frontal gyrus. The rest of the literature on the subject falls within the spectrum of these two studies with some finding that late second language acquisition simply maintains cognitive skills while others show improvements that were similar to controls that participated in different tasks such as games (Valis et al, 2019; Wong et al., 2019).

While there is a large body of research that addresses cognitive function and functional connectivity in language areas, there is not much research that has been done on the default mode network which is a collection of important brain areas that have spontaneous brain activity at rest (Sheline et al., 2010). We hope to contribute to this literature to help expand the body of knowledge on the effects of second language acquisition in older populations by exploring this less addressed perspective.

Our experiment consisted of 53 healthy adults ranging from 43 to 80 years old, divided into an experimental (n=30) and control (n=23) group. The experimental group participated in a semester long, social Spanish class that met 3 times a week. These subjects were administered a memory test as well as a resting state functional MRI exam before and after the language class. We looked specifically at the default mode network to see if there were any changes in these important brain areas. This network has been found to align with the first regions affected by Alzheimer's disease (Greicius et al., 2004). The changes in functional connectivity within this network have been found to differ within patients with brain amyloid deposition or phosphorylated tau proteins prior to any manifestations of cognitive or behavioral decline and therefore serve as an important marker for the onset of Alzheimer's disease (Sheline et al., 2010; Wang et al., 2013). By analyzing the functional connectivity of this network, we will be able to detect if there are any changes in these regions implicated in Alzheimer's disease associated with participation in the Spanish class in the middle to older aged subjects that may increase cognitive reserve. In addition, we also compared the memory scores with the functional connectivity data to see if there is any correlation between the two.

Methods

Participants and Recruitment

The experiment consisted of 53 healthy adults ranging from 43 to 80 years old. There were 39 women and 14 men. The experimental group, who underwent a semester long, social Spanish class where they met 3 times a week, consisted of 3 men and 27 women. This left the control group at 11 males and 12 females making it much more balanced than the experimental group. The average age of participants was 57 and 42% had earned a 4-year degree. In addition, 19% had completed some college and 9% had completed a 2-year degree.

The participants were recruited from various places, including through flyers on bulletin boards on BYU campus as well as at the Provo Recreation Center and Orem Senior Friendship center. An email was also sent to the researchers' acquaintances with information about the study seeking more participants. Others were also recruited through the direct request of researchers. All participants were offered $20 dollars in compensation as well as a free Spanish course with permanent access to the materials used in the class.

In total, there were 120 responses, which were then narrowed down during two introductory meetings which only about 80 people attended. During these meetings, the attendees were assessed to ensure they fit the following criteria: they were monolingual, met the psychological and safety requirements for an MRI, and were 40 years of age or older. Specific criteria for the exclusion of participants due to the MRI included: non-MRI compatible metal in their body, pregnancy, a weight over 300 pounds, tattoos from non-reputable sources, history of neurological disease or conditions, left-handedness, past brain trauma, claustrophobia, and mood or psychiatric disorders. 8 participants were disqualified specifically due to MRI safety.

Assessment of whether or not a participant was monolingual was determined through a screening questionnaire. They were asked to identify if they had learned a second language in their life as well as their proficiency. 7 participants identified extensive experience in a second language and were disqualified. The others then underwent additional screening designed with the proficiency standards of the American Council on the Teaching of Foreign Languages to test language skills at the advanced, intermediate and novice levels. All remaining participants were assessed as novice at best.

The control group consisted mainly of people who were originally interested but were unable to participate in the experimental group due to conflicts in their schedule as well as people recruited by those initially asked to be in the control group. 15 of them were asked to participate in the control group and 15 accepted.

In the end, data was used from subjects who had MRI data and memory scores for both time points which resulted in 41 subjects. One subject only had 9 of 64 test trials, so the data for that subject was removed from the analyses. There were also 4 participants that had more than 10 absences who were excluded. A few others did not have both memory scores and were excluded as well.

Language Course

The language course was held on the Brigham Young University campus, lasting 3 months and occurring at two different times, 10 am and 5 pm, to accommodate the participants' schedules. The course itself was held entirely in Spanish and participant agreed to a strict no English rule during class. Each day consisted of a welcome, warm-up, new material, activities, and a homework assignment. The class referenced *Unidos* second edition, published by Pearson, for grammar and cultural instruction.

Behavioral Task

The participants underwent a behavioral task called the Mnemonic Similarity Task, which is a highly sensitive tool for assessing memory and hippocampal integrity. It works by placing strong demands on pattern separation. First, the participants perform an incidental encoding task, where they make binary determinations between a category. Immediately after, they undergo "a surprise recognition memory task in which they must identify each item as 'old', 'similar', or 'new' . . . One-third of the images in the test phase are exact repetitions of images presented in the study phase (targets), one-third of the images are new images not previously seen (foils), and one-third of the images are perceptually similar to those seen during the study phase, but not identical (lures)" (Stark et al., 2019). These lures also differ in degree of mnemonic similarity which allows the calculation of lure discrimination performance "by calculating the difference between the probability of giving a 'similar' response to the lure items minus the probability of giving a 'similar' response to the foils to account for any bias the participant may have in using the ‘similar’ response overall.” This measurement is known as the Lure Discrimination Index (LDI). Another measurement that we use in this paper is the Target Discrimination Index (TDI), which is found by taking “the difference between the rate of ‘old’ responses given to the target items minus the corresponding rate of ‘old’ responses given to the foils (a.k.a. hits minus false alarms).” The TDI has been found to not be significantly correlated with hippocampal integrity, while the LDI has found to be highly correlated with hippocampal function.

MRI Scanning

A 3T Siemens TIM Trio MRI scanner (Erlangen, Germany) with a 32-channel head coil at the BYU MRI Research Facility was used to produce a structural MRI scan the brain of each participant at the beginning and end of the language course. Structural scans used a T1-weighted MP-RAGE sequence with the following parameters: TR=1900ms; TE=2.26ms; acquisition matrix: 215 × 256; field of view=218 × 250mm; slice thickness=1.0mm; voxel size=.977 × .977 × 1.0mm; flip angle=9°; and number of slices=176; GRAPPA factor=2. All MRI scans were imported from DICOM to NIfTI file format using program dcm2nii (v. 1JUNE2015). As part of the file conversion process, structural scans were reoriented to the nearest orthogonal using rigid-body transformation and extraneous field of view was cropped. Following conversion to NIfTI format, fMRI data were distortion corrected and a motion correction was calculated based on the functional volume with the lowest number of outlier datapoints. The structural scan was skull stripped and then co-registered to the functional data and a spatial transformation was computed to transform the data to MNI template space. The motion correction and spatial normalization transformations were applied simultaneously resulting in a single data interpolation. A mask was created for each subject based on the extent of coverage of the fMRI scans. Functional data were blurred with a 4mm FWHM Gaussian blur and scaled to have a mean of 100. A principal components analysis (PCA) was conducted to remove signal from the cerebral spinal fluid (CSF) in order to collapse that signal into the baseline of the single-subject regression analysis. The regression analysis included regressors for motion (three translations and three rotations) and their first derivatives and polynomial regressors to account for scanner drift. Any large motion events were excluded from the analysis. A time series was then extracted from a seed region defined as the posterior cingulate cortex bilaterally. Functional connectivity was then calculated as the correlation between each voxel's time series and that of the seed region. Connectivity scores were z-transformed and entered into a t-test versus 0 to identify regions with significant functional connectivity with the PCC. Significant clusters were identified as those with a voxel-wise $p<.000001$ and spatial extent $k=300$. Z-transformed correlations (i.e., connectivity scores) were extracted from each significant cluster for each subject's pre- and post- scan.

Data Analysis

For the analysis, we calculated the differences in performance in both LDI and TDI at the end of the program. This was done for both the experimental and control groups, which were then evaluated through a t-test to see if they were statistically different. The MRI data was measured through the mean functional connectivity scores of nine different regions of interest (ROI). The seed region was the posterior cingulate cortex and the regions analyzed included the posterior cingulate cortex (PCC), left and right lateral temporal lobe, left and right lateral parietal lobe, right postcentral gyrus, left and right hippocampus, and left medial prefrontal cortex (MPC). The change in functional connectivity for each ROI was recorded for both the control and experimental groups and were then compared using a t-test. The functional connectivity changes were then checked for correlation with the memory scores by calculating a correlation coefficient. These correlation coefficients were then compared between the control and experimental groups using a Fisher's *r* to *z* transformation, which turns correlation coefficients into z scores allowing them to be compared and analyzed for statistical significance by determining the observed *z* test statistic (Comparing Correlation Coefficients, n.d.). This value was then converted to a p-value.

Results

Analysis of the fMRI functional connectivity scores demonstrates the effects of the language course on changes in the default mode network pre- and post-testing. The Mnemonic Similarity Task provides data on if the language course helped with memory performance from pre- to post-testing. Then, comparing the two change values for correlations will provide the needed information to determine whether or not the changes in functional connectivity are related to the memory performance of the participants.

Functional Connectivity

After setting the seed region for the posterior cingulate cortex, the functional connectivity data showed that there were differences in the control and experimental group. The change in functional connectivity for each of the nine different regions of interest decreased slightly in the control group from start to finish. This is contrasted with an increase in seven of the nine regions in the experimental group, while the other two regions, the left and right hippocampus, stayed basically the same. The one-degree-of-

Table 1	PCC	L Lat Temp	L Lat Par	R Lat Temp	R Lat Par	R Post Central	L Hipp	R Hipp	L mPFC
Control	-0.0157	-0.0205	-0.0352	-0.0011	-0.0132	-0.0123	-0.0262	-0.0233	-0.0098
Experimental	0.0271	0.0077	0.0304	0.0149	0.0162	0.0119	-0.0025	-0.0032	0.0368
P-Value	0.0409	0.0712	0.0141	0.2405	0.2280	0.2333	0.1097	0.1551	0.0370

Figure 1

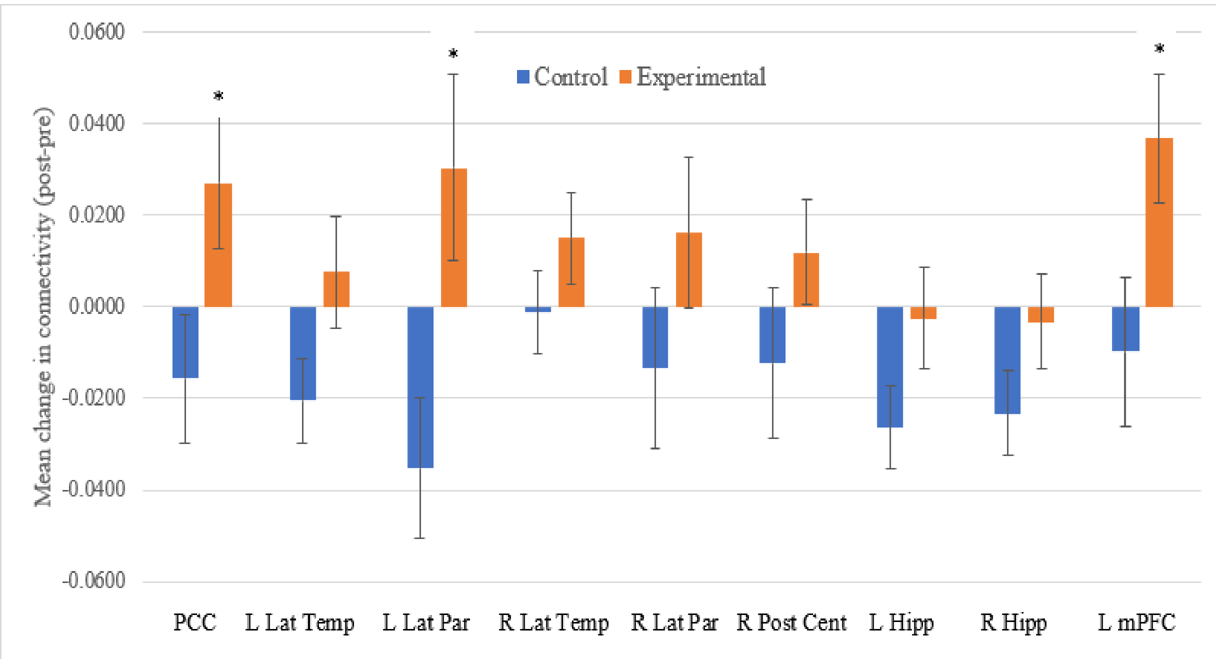

Table 1 and Figure 1 – Average change in functional connectivities for regions of interest
Mean functional connectivity changes after language course for control and experimental groups. Table 1 shows p-values of the differences between the two groups for each ROI. Highlighted values and * for p-value < 0.05

freedom contrast for each region of interest between the control and experimental groups was significant in three of the nine regions at the $p < 0.05$ level. These regions were the posterior cingulate cortex (PCC; $p = 0.041$), the left lateral parietal cortex ($p = 0.014$), and the left medial prefrontal cortex ($p = 0.037$). Though following the trend of a greater functional connectivity in the experimental group, the other six areas were found not to be statistically significant.

Mnemonic Similarity Task

Performance on the Mnemonic Similarity Task was measured before and after the language class with a focus on the participants' LDI and TDI. Figure 2 shows the overall changes in performance on the task for both LDI and TDI. Both the control and experimental groups showed a small increase in performance in LDI. In contrast, the TDI scores for the control group showed a small increase while the experimental group decreased in performance. Upon further analysis with a t-test, it was found that the differences between the control and experimental groups for both the LDI and TDI were not statistically significant.

Table 2

	ΔLDI	ΔTDI
Control	0.0647	0.0124
Experimental	0.0848	-0.0900
P-Value	0.7544	0.0978

Figure 2

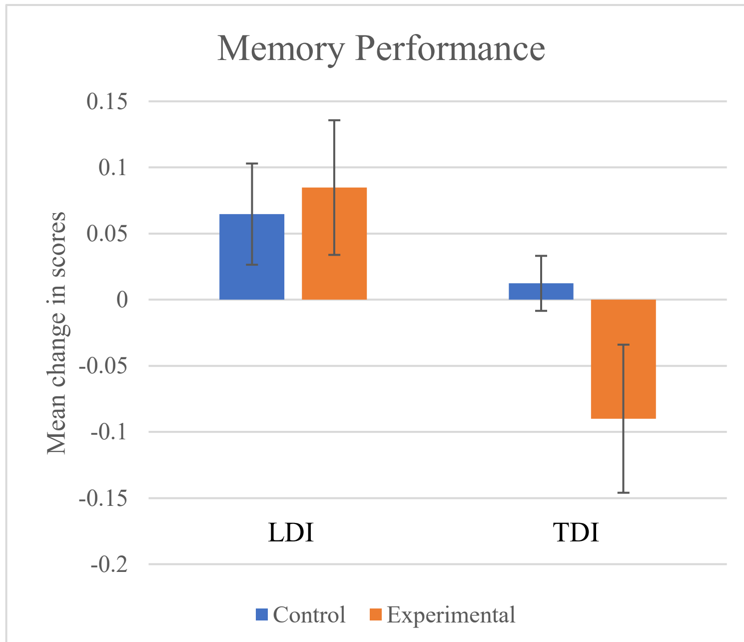

Table 2 and Figure 2 – Average differences in LDI and TDI
Mean changes in LDI and TDI for the control and experimental groups. Table 2 shows p-values for the differences between the control and experimental groups.

Memory and Functional Connectivity Comparison

The next relationship we observed was whether or not the change in functional connectivity of the regions of interest were related to the memory scores. To do this we calculated the correlation between the change in LDI/TDI and the change in functional connectivity for each score. In the control group, the LDI correlations were all negative and moderately strong ranging from -0.25 in the left mPFC to -0.69 in the PCC. The experimental group gave only weak correlations except in the case of the PCC which was moderate with a negative correlation of -0.41. The TDI scores for the experimental group were all weakly correlated with the functional connectivity scores for all ROIs, while the control group was weakly to moderately correlated. The correlations for both the LDI and TDI results were then converted to z-scores and the differences between the control and experimental groups for each region of interest were tested for significance and converted to p-values to test whether the differences in correlations between the control and experimental groups were significant. None of differences in the correlations for ROIs in both groups were found to be significant.

Table 3 Correlation between LDI and Functional Connectivity Scores

	PCC	L Lat Temp	L Lat Par	R Lat Temp	R Lat Par	R Post Central	L Hipp	R Hipp	L mPFC
Control	-0.6938	-0.5090	-0.4624	-0.3691	-0.3447	-0.5929	-0.4077	-0.3116	-0.2517
Experimental	-0.4140	-0.1862	-0.2821	-0.1839	-0.1441	-0.2218	-0.1369	-0.0834	-0.1914
P-Value	0.1146	0.1398	0.2710	0.2797	0.2673	0.0928	0.1962	0.2446	0.4271

Table 4 Correlation between TDI and Functional Connectivity Scores

	PCC	L Lat Temp	L Lat Par	R Lat Temp	R Lat Par	R Post Central	L Hipp	R Hipp	L mPFC
Control	-0.1094	0.0332	-0.3482	0.0309	-0.4062	0.2220	0.3767	0.1884	0.3511
Experimental	-0.0908	0.0010	-0.1172	-0.0104	-0.0526	0.1404	0.2171	0.1247	-0.1014
P-Value	0.4783	0.5372	0.2382	0.5477	0.1364	0.5967	0.6946	0.5750	0.9127

Tables 3 and 4 - Correlation between LDI/TDI and Functional Connectivity Scores
Shows correlations between mean memory performance differences between pre and post-test and the changes in the functional connectivity for the nine different ROI. Table 3 uses LDI and Table 4 uses TDI.

Discussion

In the control group, each of the nine different ROIs showed, on average, decreased functional connectivity from the beginning of the program to the end. This unanimity demonstrated the anticipated, normal decline in connectivity that would occur over this period. In contrast, the experimental group experienced a universal increase in all ROIs except the hippocampus. Though only three of these differences ended up being significant, the universality of the decrease in the control group and the increase in the experimental group suggests more research should be done over a larger time frame to provide more data to see if the default mode network through a language course improves just the three areas observed in this study or the entire network.

Two of the three ROIs with significant connectivity increase, the PCC and inferior parietal lobes, were identified directly by Greicius et al. (2004) as having decreased metabolism early in the onset of Alzheimer's disease. The results of this study support the findings of Bubbico et al. (2020) that second language acquisition increases functional connectivity and could potentially help prevent the onset of Alzheimer's disease. More research is needed to confirm these results, but this data provides additional evidence in support of language learning at an elderly age being a helpful intervention for the prevention of Alzheimer's disease. Future studies should also seek to distinguish between the effects of social interaction and language learning due to the social interactions during class being a possible confounding variable.

The results of the Mnemonic Similarity Task showed that the language class had no significant impact on the participants memory as measured by the LDI and TDI. This lack of improvement agrees with the research of Klimova et al. (2020), who found a lack of cognitive enhancement after a language class. Since the duration of the experiment was only three months and there was no long term follow up, it is difficult to determine whether or not the class had any effect on maintaining or sustaining memory skills, but, over the course of the class, the controls showed no signs of declining memory skills, and the experimental group showed no significant improvements.

Possible confounding factors include a ceiling effect caused by nearly half of the participants having earned a 4-year degree and the unknown intellectual engagement of the control group. Many participants were assigned to the control group because they were too busy to participate in the class, so it is possible these other activities provided a similar benefit to their memory as the language course leading to a lack of difference in the memory scores. An additional limitation to this analysis is that we only analyzed memory, while other mentioned experiments utilized more comprehensive cognitive evaluations. Future research should seek to do both to have more data points to consider.

Our final analysis looked at comparing the change in functional connectivity in the default mode network to the change in LDI and TDI to see if they were correlated and then if the correlations between the control and experimental groups were significantly different. All of the memory correlations for both the experimental and control groups were negative for LDI, which suggests that the default mode network decreases in connectivity as memory skills increase. These negative correlations could be caused by an increase in efficiency in processing, but it is unclear. Since differences in correlations between the control and experimental groups for both LDI and TDI were not significant, the changes in the functional connectivity from the single, semester-long language course did not have any apparent effect on the memory scores. Accordingly, the functional connectivity for the hippocampus did not change over the course of the class, so it is logical that the LDI, which is a sensitive tool for assessing hippocampal integrity, would not be affected either. This suggests that the benefits of a language course may be independent of memory performance and possibly other forms of cognition as well. Further research is needed to confirm whether this is true or not.

An additional limitation to these results was the lack of males in the experimental group. While there are no differences in overall intelligence between men and women, each sex does have slight advantages in certain types of memory. Men tend to have better spatial memory, while women perform better in tests of verbal fluency and memory. Women also generally have more severe cognitive decline and dementia with Alzheimer's (Hamson et al., 2016). Since all of the participants were healthy and the Mnemonic Similarity Task tests object recognition and not spatial or verbal memory, then the lack of males in the experimental group should not have an effect on the memory results.

There are also sex differences in the default mode network that may limit the reliability of the data. As age increases, the differences in the default mode network between males and females increase as well. Differences have been found in six of the nine ROI including the PCC, prefrontal cortex, hippocampus, and temporal lobes (Conrin et al., 2018). These differences could have created the observed differences between the experimental and control groups, but more research is needed to determine whether or not it had an impact.

In conclusion, the functional connectivity indicates that the language course increased the functional connectivity in key structures associated with Alzheimer's disease, indicating that it could be a possible preventative measure against the disease. In contrast, the memory scores were not affected by the language course showing that the effects may not extend to certain cognitive measures. The lack of difference in the correlations between the functional connectivity changes and the memory scores of the control and experimental groups confirm that the benefits of the language course may not extend to memory.

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