AGE, GENDER, AND APOE4 RELATED DIFFERENCES IN SPONTANEOUS COGNITION: AN ADAPTED THINK ALOUD PARADIGM

By

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Abstract

It is of utmost importance to understand the cognitive differences between healthy and unhealthy aging in humans as Alzheimer's disease (AD) quickly becomes a devastatingly common reality for rapidly aging populations worldwide. To understand these changes, this study compared the spontaneous thoughts of two cohorts – one consisting of younger adults, and one consisting of older adults – as both cohorts spoke aloud anything that came to mind for a ten-minute period. This study explores differences between key constructs of positive valence, negative valence, and internal/external focus expressed in spontaneous thought to help inform our understanding of the aging process. These analyses of spontaneous thoughts were examined in combination with gender and AD-risk factors beyond age, including genetic markers and mental health questionnaires. The results found slightly diverged from our hypotheses, but overall there was still support for many of the concepts we expected to see. The genetic risk factor results showed an interesting trend for young adults where their status affected their level of negativity. We hope this study can serve to build more of a foundation for aging research and encourage more research in this area due to its impact.

1. Introduction

Although many studies have investigated the aging mind, there is still much to be discovered about the mechanisms underlying healthy and pathological aging in humans. Prior work has not clarified how deviations in the ways thoughts arise and unfold spontaneously may signal abnormal aging processes such as preclinical Alzheimer's disease (AD). In order to uncover more about these aging processes, the current study aims to use an adapted Think Aloud paradigm in which participants give us access to their verbalized spontaneous thoughts over the course of a ten-minute session. In combination with consideration of AD risk factors, which are measured with genetic testing as well as questionnaires, we hope to illuminate the characteristics of healthy and unhealthy cognitive aging by examining these internally guided thoughts which are thought to be a product of the Default Mode Network (DMN), which is one of the first places where AD pathology takes hold in the brain (Sperling et al., 2009). By quantifying these constructs of positivity, negativity, and internal/external focus, we can investigate the changes that may be occurring between age groups, genders, and between people with differing APOE4 statuses to further the understanding of how those factors and other risk factors could influence the content of spontaneous thought.

Positivity Effect

Despite cognitive and physical challenges associated with aging, numerous studies suggest that well-being paradoxically improves as part of the typical aging process. This increase in well-being has been linked to positive changes in mood, memory, and social relationships. The Positivity Effect proposes that there is a mental shift in older age where people are more inclined to remember the positive aspects of their life, such as happy moments or memories, creating an attentional bias (Kennedy et al., 2004). This is hypothesized to be the case because focusing on

the positive elements of life better serves the emotional well-being of older adults. Understanding sources of the Positivity Effect and the increase of well-being seen in *normal* aging can help us identify *abnormal* aging processes, including those related to AD and AD risk.

The Role of the DMN

The DMN plays an important role in internally directed cognition, including spontaneous thought and non-task related thought (Andrews-Hanna et al., 2019). Thus, cognitive tasks that draw on these internal processes may be promising as cognitive markers of early AD and AD risk. The Think Aloud task is a measure of spontaneous thought where people vocalize whatever comes to mind (Raffaelli et al., 2020). We reasoned that this task might be sensitive to normal and abnormal brain changes in the DMN due to the non-task related nature of the Think Aloud protocol. The DMN has been identified as one of the first brain networks where AD pathology occurs, therefore making it an important target of study (Sperling et al., 2009). Depression and the apolipoprotein E e4 (APOE4) allele – two established risk factors for AD – have also been linked to alterations in the DMN, giving more emphasis to the importance of studying this brain network and its role in the aging mind (Harerimana et al., 2021; Kaiser et al., 2015).

Mental Health Risk Factors

Depression is a mental health condition characterized by excessive negative thought patterns and considerably lower quality of mental health. In many cases, the devastating impact of this negative cycle for the individual leads to a lower quality of life and a myriad of other issues. Depression has been linked to Alzheimer's risk in prior literature although the full relationship between these two is not entirely clear (Harerimana et al., 2021).

Genetic Risk Factors

Although AD seems to have a complex genetic basis, there is one genetic component that is very strongly linked to the development of AD; this is the APOE4 allele. As with much of AD work, it is still unclear how this protein can so drastically increase one's predisposition to developing AD, but there certainly seems to be a strong link (Corder et al., 1993).

Internal/External Focus

The construct of internal and external focus stems from the functions of the DMN. Since the DMN is an internally directed cognition network and the DMN is one of the first compromised brain regions with AD (Andrews-Hanna et al., 2019; Sperling et al., 2009), we developed this construct to examine how internal or external participants' thought processes were with the aim of seeing if there are any changes with aging or APOE4 status. Internal thoughts have to do with thoughts and memories, whereas external thoughts have to do with perceptions of the five senses, such as what the participant sees or hears in their environment. Prior literature suggests that older adults may tend to be less internal and more external than younger adults (Turnbull et al., 2021). However, the Turnbull study in 2021 had participants engage in a task to collect their data, and there is no task in the current study, so it will be interesting to see if this trend holds true.

Gender Effects

Prior literature has explored possible gender differences in how APOE4 impacts the brain. The exact reasons for this difference are unknown, however. Women with the APOE4 allele are significantly more likely to develop AD pathology than men who carry this allele (Altmann et al., 2014). Therefore, we also looked for thought pattern differences between the genders.

Hypotheses

The Positivity Effect informs our hypotheses that older adults will be more positive across many measures and less negative, and that they will have a higher quality of wellbeing overall. We also expect to see differences in the constructs of negativity, positivity, and internal/external focus when comparing older and younger adults that will help us understand the cognitive shift that may be occuring in aging. Finally, we hypothesize that due to the pathological link of APOE4 and AD, there will be a difference in the performance on certain constructs based on APOE4 status; for example, that APOE4 carriers may be more negative and more depressed. We think this will be even more prominent in the older age group as these participants are closer to the age where we would expect to see AD symptom onset.

2. Methods

For this study, 50 cognitively normal older adults (OA) (mean 69.3 yr., 61-83, 68% female) and 53 cognitively normal younger adults (YA) (mean 22.6 yr, 18-34, 75% female) participated. Participants were recruited with a variety of measures, including online ads, University of Arizona online platforms for students, word of mouth, the End Alz Now GeneMatch database, flyers, newspapers, and other sources. The study was reviewed and approved by the University of Arizona Internal Review Board. Statistical analyses were completed using Jeffrey's Amazing Statistics Program, more commonly called JASP, which is an R based statistical program (JASP, 2022).

Cognitive status was evaluated for younger adults using the WAIS vocabulary and similarities and the MOCA. For older adults, a more comprehensive neuropsychological battery was administered, including the WAIS vocabulary and similarities, Rey Complex Figure Test, Trail

Making Test Paths A and B, Boston Naming Test, CVLT, Matrix Reasoning Test, Digit Span Test, and the FAS. All participants were within normal cognitive abilities.

Exclusion criteria included previous severe head injuries, incidents of fainting or lost consciousness for significant periods of time, past seizures and strokes, severe mental illness, severe drug or alcohol use, limited English proficiency, and psychiatric medications if the participant was not fully adjusted to the medication. Participants were screened by phone to ensure they had not sustained significant brain damage in the past and that their cognitive abilities seemed intact.

OA mean age	69.3
YA mean age	22.6
OA % female	68%
YA % female	75%
OA avg yrs edu	17.8
YA avg years edu	15.3
race/ethnicity: White	81.10%
race/ethnicity: Hispanic or Latino	7.90%
race/ethnicity: Asian	6.90%
race/ethnicity: Black or African American	2.90%
race/ethnicity: Native American	0.90%

Table 1: Sample Demographics*. Age, gender, education, and race/ethnicity breakdown of the sample. OA is categorized as adults from 61-83 years old and YA is categorized as adults from 18-34 years old. Note for race/ethnicity: only 97 out of 103 participants shared their ethnicity.*

Participants were also asked to complete all tasks remotely with minimal in-person interaction with the interviewer due to the extenuating circumstances of COVID-19. Zoom for Healthcare, a HIPAA certified Zoom platform, was utilized as a resource for the interviews conducted in this study.

Session 1:

Prior to behavioral sessions, participants were deidentified and given neuropsychological assessments to confirm their mental capacities were within normal limits. None of the tasks from Session 1 are relevant to this current study. Participants are told at the end of this session when they will have their genotyping kit that measures their APOE4 status delivered. They are also reminded that we cannot disclose their APOE4 results to them as it was determined to be an ethics violation.

Session 2:

Participants started this second session by filling out more questionnaires on REDCap, a secure platform for data collection. Then, they were guided through an Affect and Arousal grid to get a baseline of how they were feeling at the beginning of the session. Next, the Think Aloud task was conducted.

For this study, the Think Aloud resting state paradigm was used (Raffaelli et al., 2020). This task consists of participants being presented with a standard black screen with a crosshair on it. Participants were given these instructions verbatim: "I would like you to perform a type of 'think aloud' task that will consist of you simply voicing out loud whatever comes to your mind for 10 minutes. You'll be asked to simply sit here in your room for 10 minutes and speak aloud your thoughts continuously as they are occurring. During this task, you may notice that at times, your attention might be oriented outwards towards the sights and sounds of your external environment. At other times, you may be thinking internally, about a particular topic, or your attention might be oriented towards your feelings, bodily sensations, and emotions. Regardless of what comes to mind at different moments in time, I would like you to continuously voice out

loud what's on your mind at that moment in time. I will be unable to hear what you say. The person that transcribes your audio will not know your name and will not be the experimenter that was present during your experimental session. In summary, I ask that you remain awake and simply voice out loud whatever you are experiencing."

Participants were read these instructions over Zoom and then were guided through displaying a plain black screen on their computer as big as possible. The black screen was utilized to help control the stimulus for each participant. Due to the experimental sessions being conducted over Zoom, participants logged in from varying locations and although their environment could not be controlled in the same way it could be if the sessions were in a laboratory environment, we tried to create some sort of unity. Then, to provide privacy, the experimenter turned off their video and audio to allow the participant to feel the most comfortable and willing to share the truest form of their thoughts. After the Think Aloud, they were again asked to rate their emotions on the Affect and Arousal grid.

Next, participants were led through the genotyping procedure where they collected spots of blood on a bloodspot card to be sent in and tested for APOE4 allele status. This was done using a blood spot card and self-collection methods.

A myriad of questionnaires were also administered: a demographics form, Functional Activities Questionnaire, Prospective and Retrospective Memory Questionnaire, Death Attitude Profile, Big Five Personality Inventory, Emotion Regulation Questionnaire, Rumination Reflection Questionnaire, Mindfulness Attention and Awareness Scale, PHQ-9, Revised UCLA Loneliness Scale, Spontaneous Deliberate Mind-Wandering, a Goals assessment form, Positive and Negative Affect Schedule, SUDS, a Coping Strategies form, SF-12, Pittsburgh Sleep Quality

Index, Multidimensional Scale of Perceived Social Support, and Ryff Scales of Psychological Wellbeing. These questionnaires assessed well-being and individual differences in AD risk factors. Notably, the PHQ-9 was used to measure depression and is analyzed further in this paper.

Rating Methods

As previously discussed, during the Think Aloud task, participants voiced aloud their continuous stream of thought alone and at rest for ten minutes. This Think Aloud task was audio recorded and transcribed for analysis. The audio recordings were then rated continuously by experimenters on content characteristics such as negative valence, positive valence, and internal versus external focus.

Positive valence is the amount of positivity present at varying times over the course of the task in addition to the perceived emotional tone of the participant. These constructs were all rated dynamically and in real time, so as participants drifted from one topic to another, raters would adjust the score accordingly. Positivity was rated on a scale of 0 to 1, where raters would use a slider to dynamically rate the behavioral data and adjust the rating along a scale using an originally coded script in the program PsychoPy, which gave us results in the form of a csv file that contained all of the ratings as well as the exact time the rating occurred (Figure 1). The rating process was completed by two different raters for each construct and the final results used for analyses are an average of both of these independent raters' scores.

	0	0.25	0.5	0.75	1
	No Positivity	Slightly Positive	Moderately Positive	Very Positive	Extremely Positive
	"Today is Tuesday"	"I had Starbucks"	"I had a nice time with friends"	"I aced my test!"	"I got the job!!"
	Neutral or no goodness	Make a bad day better goodness	Casual goodness	Extra/atypical goodness	Life highlight goodness
Content of thought	Meh	OK	Good	Great	Amazing
	Bad/Negative	Fine	Pleasant	Noteworthy	Extraordinary
Emotional tone	Bummed, annoyed, frustrated, angry, sad, etc.	Comforted/soothed	Happy/glad	Delighted	Joyful/euphoric
		Optimistic	Upbeat	Enthusiastic	Exuberant
		(somewhat) appreciating	(generally) enjoying	(quite) satisfying	(deeply) fulfilling

Figure 1: Positivity Valence Rating Guide. *Example of positivity rating guide given to raters to help them determine the level of positivity of statements and to keep ratings across participants and between raters consistent.*

Negative valence was rated the same way as positive valence, with 0 being no negativity and 1 being the most negativity expressed.

	0	0.25	0.5	0.75	1
	No Negativity	Slightly Negative	Moderately Negative	Very Negative	Extremely Negative
	"Today is Tuesday"	"I was almost late to class"	"This noise is really annoying and disruptive"	"I crashed my car"	"It was the worst day of my life!"
	Neutral or no misfortune	Slight misfortune, could make their day worse	Casual misfortune	Extra/atypical misfortune	Traumatic or one of life's low points
Content of thought	Meh	Annoying	Lousy	Bad	Terrible
	Good/Positive	Bothersome	Unpleasant	Noteworthy	Dispair/grief
Emotional tone	Happy, excited, upbeat, optimistic, etc.	Bummed	Frustrated	Angry/mad	Furious
		Uncomfortable	Anxious	Sad	Hopeless/Distraught
		(somewhat) pessimistic	(generally) unfavorable	(very) unsatisfying	(deeply) upsetting

Figure 2: Negative Valence Rating Guide. *Example of negativity rating guide given to raters to help them determine the level of negativity of statements and to keep ratings across participants and between raters consistent.*

Internal and external focus was rated slightly differently. A rating of 0 indicated an entirely external focused thought and a rating of 1 indicated an entirely internally focused thought. For example, an internal thought would be “I feel happy” and an external thought would be “I see a bird outside my window”. This construct was also dynamically rated as raters listened to the audio, so there is room for thoughts to be somewhere in between the rating of 0 and 1.

<table>
<tr><th></th><th>0</th><th>0.25</th><th>0.5</th><th>0.75</th><th>1</th></tr>
<tr><td></td><td>Entirely external</td><td>Mostly external, slightly internal</td><td>Equally external and internal</td><td>Mostly internal, slightly external</td><td>Entirely internal</td></tr>
<tr><td></td><td>(current) physical environment and/or physical sensations</td><td>Mostly physical, some mental/psychological</td><td>Equal mix of physical and mental/psychological</td><td>Mostly mental/psychological, slightly physical</td><td>Mental/psychological processes</td></tr>
<tr><td rowspan="3">Thought content</td><td>Sights</td><td rowspan="3">Some emotionality or intention, but mostly focused on current perception or sensations</td><td rowspan="3">Feelings/memories/intentions that are tied to physical stimuli and vice versa</td><td rowspan="3">Feelings/memories/intentions with some mention of current perception or sensations</td><td>Memories</td></tr>
<tr><td>Sounds</td><td>Intentions</td></tr>
<tr><td>Bodily sensations</td><td>Feelings</td></tr>
<tr><td>Examples</td><td>"This noise is really loud"</td><td>"That noise is annoying. I wish it would stop"</td><td>"That picture reminds me of the time my friends and I..."</td><td>"I remember last month laying in the hospital bed, kind of like laying this MRI"</td><td>"I'm really excited about my plans this weekend"</td></tr>
</table>

Figure 3: Internal/External Valence Rating Guide. *Example of internal/external rating guide given to raters to help them determine the level of internal/external focus of statements and to keep ratings across participants and between raters consistent.*

To help understand these ratings in action, here is a sample quote from a participant to demonstrate.

“…Um, funny that the six months I was with my parents we had the greatest times!…Uh I just felt a lot of comfort and then of course after that is a lot of horrible disgusting pain which never really goes away it just kind of fades a little at a time…”

This quote would be rated highly internal all the way through since they're talking about emotions. The first part of the quote would be rated as slightly positive starting at "funny" and go up to highly positive when they're talking about how it was the "greatest times" and how they felt "comfort". Then this would be rated highly negative when they talk about the "horrible disgusting pain" from their parents' death.

An example of a highly external thought would be if participants described their immediate surroundings and talked about what they were seeing or hearing at that moment. Many participants did this in their Think Aloud.

4. Results

Overall, older adults' thoughts were numerically, but non-significantly, more positive than younger adults' thoughts (Figure 4, p=.09). Not only were older adults more positive than younger adults, but they were also significantly more positive than they were negative during the course of the Think Aloud (Figure 4, p=.007).

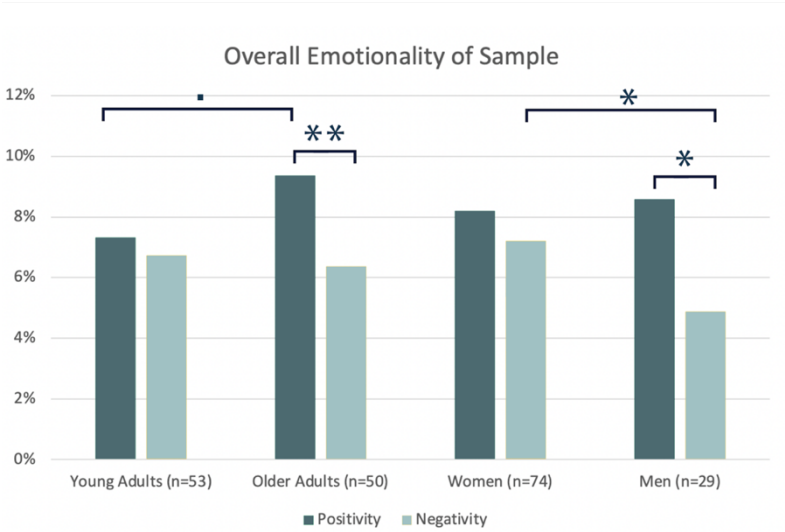

Figure 4: Overall Emotionality of Sample. *Comparison of the mean positivity and negativity of the whole sample during the Think Aloud task, separated by age group and gender. The y axis*

*represents percent of the Think Aloud task that was rated positive or negative by independent raters. .= p is close to .05 but not quite, *=p<.05, **=p<.01.*

Additionally, younger adults were significantly more depressed as measured by the PHQ-9 than older adults (not pictured, p=.021).

Across the sample, women tended to be significantly more negative than men (Figure 4, p=.03), and men were significantly more positive than they were negative during the course of the Think Aloud (Figure 4, p=.017). However, when age was factored in, young women were especially more negative than their young male counterparts (Figure 5, p=.04). Young women were also significantly less positive than young men (Figure 5, p=.01) and young women were less internal than young men (Figure 6, p=.009). In contrast, older women were significantly more positive than their older male counterparts (Figure 5, p=.052)

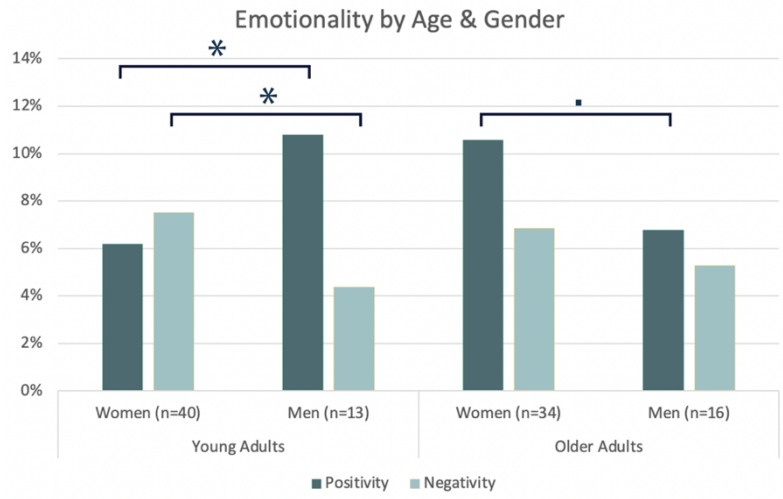

Figure 5: Emotionality by Age and Gender. *Comparison of the mean positivity and negativity of the sample during the Think Aloud task, broken down by age group and then further separated by gender. The y axis represents percent of the Think Aloud task that was rated positive or negative by independent raters. .= p is close to .05 but not quite, *=p<.05.*

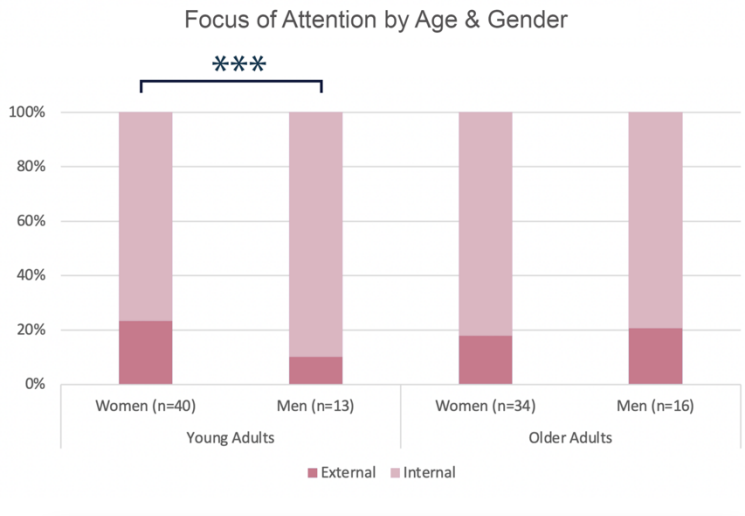

Figure 6: Focus of Attention by Age and Gender. *Comparison of the mean internal and external focus of the sample during the Think Aloud task, broken down by age group and then further separated by gender. The y axis represents percent of the Think Aloud task that was rated internal or external by independent raters. ***=p<.001.*

Across the group, participants who carried the APOE4 allele tended to be more negative than those in the study who did not carry the APOE4 allele, but the relationship was not quite significant (Figure 7, p=.066). This effect of being an APOE4 carrier and being more negative seemed to be carried by the young adults as young adults who were APOE4 carriers (n=10) were more likely to be negative (not pictured, p = 0.004) but this was not true for older adults who were APOE4 carriers (not pictured, p = 0.83, n=24).

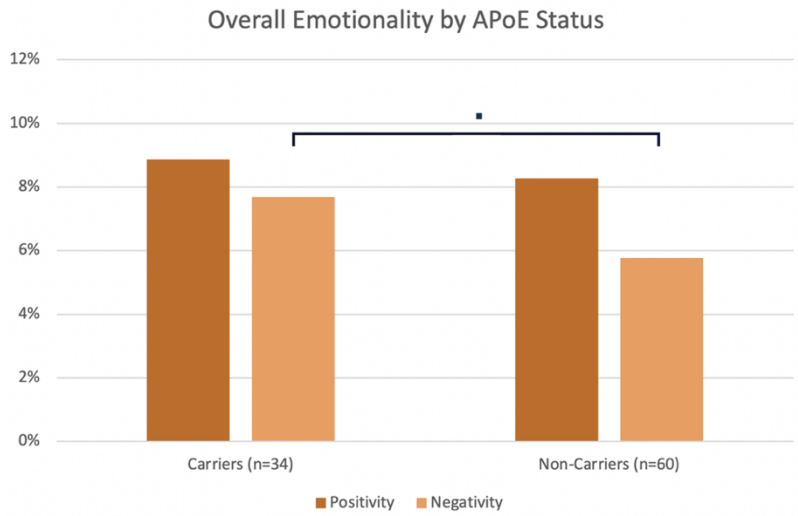

Figure 7: Overall Emotionality by APOE4 Status. *Comparison of the mean positivity and negativity of the sample during the Think Aloud task, separated by APOE4 status. The y axis represents percent of the Think Aloud task that was rated positive or negative by independent raters. .= p is close to .05 but not quite.*

The other constructs of positivity and internal/external focus as well as PHQ-9 score were examined between APOE4 carriers and non-carriers to see if there were differences in performance based on APOE4 status, but these results were not significant in the whole sample (Table 2) nor when broken down by age group (Table 3 and 4).

Measure	P Value
Negativity	0.066
Positivity	0.66
Internal/External	0.57
PHQ-9	0.26

Table 2: APOE4 Whole Sample Differences: *Differences between the scores for the constructs for APOE4 carriers and non-carriers for the whole sample.*

Measure	P Value
Negativity	0.004**
Positivity	0.86
Internal/External	0.52
PHQ-9	0.64

Table 3: APOE4 Younger Adult Sample Differences: *Differences between the scores for the constructs for APOE4 carriers and non-carriers for the younger adults. **=p<.01.*

Measure	P Value
Negativity	0.83
Positivity	0.86
Internal/External	0.3
PHQ-9	0.21

Table 4: APOE4 Older Adult Sample Differences: *Differences between the scores for the constructs for APOE4 carriers and non-carriers for the older adults.*

5. Discussion

Positivity Effect

Our study found broad support for the Positivity Effect in aging (Kennedy et al., 2004). Although older adults were not significantly more positive than younger adults, they were numerically more positive in their results. Additionally, the finding that older adults are significantly more positive than negative could support the Positivity Effect and the idea that there is a shift towards prioritizing thinking about positive aspects of life. The younger adult group was significantly more depressed as measured by the PHQ-9 than the older adult group, and while depression and positivity are not opposites, this could suggest that the older group is not experiencing as many depressive symptoms as younger adults and that could be contributing to their improved quality of life and higher rate of positivity.

Gender Differences

We found many interesting gender differences in this study. Overall, women in the sample were significantly more negative than men. However, when we break up this finding by age group, we can see how there is a difference between the effect of gender on the older and younger adult groups. For younger adults, women remained significantly more negative and significantly less positive than their male counterparts. Another surprising finding from the young adult group is that young men were more internal and young women were more external, meaning that men tended to talk more about emotions, thoughts, and memories and they talked about these things in a more positive light.

Additionally, young men were significantly more positive than negative ($p=.014$), which could reveal a bias towards positivity, as young men were not nearly significantly lower on the PHQ-9

but they were a little lower numerically (p=.4), or it could reveal a bias against negativity. Younger men may be less comfortable with expressing negative emotions due to the perceived level of vulnerability that comes along with that and the perception of masculinity in the United States still being very strongly against vulnerability, although this interpretation is speculative and the best way to understand this phenomenon would simply be to increase our sample size.

For the older adults, in contrast to the overall sample finding that women were more negative, older women were significantly more positive than their older male counterparts. They were also significantly more positive than negative (p=.009), which, just like the young males, could either indicate a bias towards positivity or a bias against negativity. For the older women, it could be a bias towards positivity and perhaps the Positivity Effect is once again at the base of this; this could be supported by the finding that older women were not nearly significantly lower on the PHQ-9 but they were a little lower numerically (p=.4). However, we must also consider that there could be generational attitudes at play which could make women of this age group less likely to want to express negativity, but this perspective is also speculative, and these attitudes were not necessarily expressed in the experiment. Again, the best way to better understand this trend would be to increase our sample size.

Overall, these gender differences could suggest that we need to take a more nuanced approach when looking at aging and consider how the normal and abnormal aging processes may be impacted by gender. However, a limitation of our study in examining these effects is that this was not a long-term study where we worked with the same people as young participants and then later as older participants. Generational attitudes and considerations as well as the perception of gender in the United States could be contributing to our findings and that must be acknowledged.

APOE4 Results

Participants who were APOE4 carriers tended to be more negative than non-carriers throughout the entire sample, but this relationship was just slightly above the threshold for significance. There were no other observable differences between carriers and non-carriers regarding measures such as positivity, internal/external focus, or PHQ-9 scores. To explore this trend further, we broke our analyses down by age group once more. We were expecting to see more of an impact of the APOE4 carrier status for older adults since they are closer to the expected age of AD onset. However, we found the opposite; young adults who are APOE4 carriers were significantly more negative than young adult non-carriers. This relationship did not hold true for older adults, as there was no difference between any of the constructs measured for older adults when compared between APOE4 carriers and non-carriers.

A possible explanation for this result could be that perhaps these young adults with the APOE4 allele who are currently showing more negativity than their non-carrier peers could be more likely to develop AD symptoms later in life. Prior literature has shown that young adults with the APOE4 allele can have functional brain deficits in much the same way as older adults with the APOE4 allele (Reiman et al., 2004). Perhaps they are using their DMN more when having these negative thought patterns (Harerimana et al., 2021) and causing more strain which could lead to AD pathology later in life. Of course, to explore this we would need to follow up with these people later in life, and that is not a current direction for this study, but this could be an interesting aging phenomenon to explore in the future with studies that are more suited to long-term follow up.

Limitations and Considerations

The biggest limitation of this study was the sample size. Although the entire sample is a good size at 103 participants, once we broke it down into gender, age groups, and APOE4 status, these sample sizes became much smaller, especially for the APOE4 results. In order to confirm the results that we found, we would need to have a larger sample size to make sure these findings still hold true.

An important consideration is that the COVID-19 pandemic was occurring during the entire time when we were collecting data from participants. Since the pandemic was occurring the entire time, we would hope this would help mitigate the effect it may have had by impacting all of the sample equally as opposed to having the pandemic start during the course of data collection, but we acknowledge that COVID-19 has not impacted every person the same and the level of concern about it has fluctuated over the course of the pandemic and thus over the course of our study as well.

Another limitation is that we had participants from multiple different generations taking part in our study. For the younger adults, their age range encompassed both Generation Z (born from 1997-2012) and Millennials (born from 1981-1996). For the older adults, their age range included Baby Boomers (born from 1946-1964) as well as The Silent Generation (born from 1928-1945) (Dimock, 2022). The generational differences in attitudes surrounding many different elements of the study, from depression/mental health to emotional vulnerability to even the concept of participating in research itself, could've had an impact on our results.

Conclusion and Future Research Directions

While many of our results numerically were similar to what we anticipated, some did not reach statistical significance. The trends found between age cohorts, gender, and APOE4 status are interesting and could in fact reveal true differences in thought patterns between these groups, due to a variety of factors, that could help us better understand the aging process, but many of these results need to be recreated with larger sample sizes to be viable. We hope that this study can serve as a jumping off point for future aging research and to show how cognitive measures of spontaneous thoughts could be potentially helpful in understanding and spotting indicators of aging.

Given that aging research and AD research is such a promising field for research currently, there are many different future research directions that could be interesting. Regarding the function of the DMN during the Think Aloud task, analyses could be done using fMRI scans to see how the DMN and other parts of the brain are being activated during the Think Aloud to reveal where in the brain some of these processes are happening and if this activation changes with age, gender, and APOE4 status.

Another possible option that we are currently working on is adding more dynamically rated constructs. One promising construct, called episodic specificity, could help us look further into the DMN. Episodic memory deficits have been linked to AD and reductions in the ability to express episodic specificity could be an early indicator of AD symptomology (Kvavilashvili et al., 2020; Grilli et al., 2018). Additionally, since the constructs are coded separately, we could overlap constructs to examine specific areas of the Think Aloud transcript that are of interest. For example, we could combine times when participants are highly internally focused, which we

expect to be highly tied to the DMN, and then within those highly internal areas of the transcript we could explore how the other constructs of positivity, negativity, and episodic specificity change in regard to age, gender, and APOE4 status.

To further the understanding of genetic factors of AD, there is fascinating research emerging about how APOE4 may not be the only allele of interest when it comes to aging and AD risk. APOE2 and APOE3 could also have effects on the aging process and prior studies have shown that APOE2 could even have a protective effect against AD (Li et al., 2020). The same experimental process used here could be used to explore the differences between these alleles if a larger sample size was procured for each allele representation. These future directions could be helpful in adding to the findings of the current study and furthering our understanding of healthy and unhealthy aging processes.

References

1. Sperling, R. A., LaViolette, P. S., O'Keefe, K., O'Brien, J., Rentz, D. M., Pihlajamaki, M., Marshall, G., Hyman, B. T., Selkoe, D. J., Hedden, T., Buckner, R. L., Becker, J. A., & Johnson, K. A. (2009). Amyloid deposition is associated with impaired default network function in older persons without dementia. *Neuron*, *63*(2), 178–188. https://doi.org/10.1016/j.neuron.2009.07.003

2. Kennedy Q, Mather M, Carstensen LL. The role of motivation in the age-related positivity effect in autobiographical memory. Psychol Sci. 2004 Mar;15(3):208-14. doi: 10.1111/j.0956-7976.2004.01503011.x. PMID: 15016294

3. Andrews-Hanna, J., Grilli, M., & Irish, M. A Review and Reappraisal of the Default Network in Normal Aging and Dementia. *Oxford Research Encyclopedia of Psychology.* Retrieved 10 Aug. 2021, from https://oxfordre.com/psychology/view/10.1093/acrefore/9780190236557.001.0001/acrefore-9780190236557-e-384.

4. Raffaelli, Andrews-Hanna, J. R., Wilson, R. C., & Chou, Y.-H. (2020). Think Aloud: Studying the Stream of Consciousness. The University of Arizona.

5. Harerimana, Liu, Y., Gerasimov, E. S., Duong, D., Beach, T. G., Reiman, E. M., Schneider, J. A., Boyle, P., Lori, A., Bennett, D. A., Lah, J. J., Levey, A. I., Seyfried, N. T., Wingo, T. S., & Wingo, A. P. (2021). Genetic Evidence Supporting a Causal Role of Depression in Alzheimer's Disease. Biological Psychiatry (1969). https://doi.org/10.1016/j.biopsych.2021.11.025

6. Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder. *JAMA Psychiatry*, *72*(6), 603. https://doi.org/10.1001/jamapsychiatry.2015.0071

7. Corder, Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., Roses, A. D., Haines, J. L., & Pericak-Vance, M. A. (1993). Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late Onset Families. Science (American Association for the Advancement of Science), 261(5123), 921–923. https://doi.org/10.1126/science.8346443

8. Turnbull, Poerio, G. L., Ho, N. S., Martinon, L. M., Riby, L. M., Lin, F. V., Jefferies, E., & Smallwood, J. (2021). Age-related changes in ongoing thought relate to external context and individual cognition. Consciousness and Cognition, 96, 103226–103226. https://doi.org/10.1016/j.concog.2021.103226

9. Altmann, A., Tian, L., Henderson, V. W., & Greicius, M. D. (2014). Sex modifies the APOE-related risk of developing Alzheimer disease. Annals of Neurology, 75(4), 563–573. https://doi.org/10.1002/ana.24135

10. JASP Team (2022). JASP (Version 0.16.2)[Computer software].

11. Reiman, E., Chen, K., Alexander, G. E., Caselli, R. J., Bandy, D., Osborne, D., Saunders, A. M., & Hardy, J. (2004). Functional brain abnormalities in young adults at genetic risk for late-onset alzheimer's dementia. *Proceedings of the National Academy of Sciences*, *101*(1), 284–289. https://doi.org/10.1073/pnas.2635903100

12. Dimock, M. (2022, April 21). *Defining generations: Where millennials end and generation Z begins*. Pew Research Center. Retrieved April 27, 2022, from https://www.pewresearch.org/fact-tank/2019/01/17/where-millennials-end-and-generation-z-begins/

13. Kvavilashvili, Niedźwieńska, A., Gilbert, S. J., & Markostamou, I. (2020). Deficits in Spontaneous Cognition as an Early Marker of Alzheimer's Disease. Trends in Cognitive Sciences, 24(4), 285–301. https://doi.org/10.1016/j.tics.2020.01.005

14. Grilli, Wank, A. A., Bercel, J. J., & Ryan, L. (2018). Evidence for Reduced Autobiographical Memory Episodic Specificity in Cognitively Normal Middle-Aged and Older Individuals at Increased Risk for Alzheimer's Disease Dementia. Journal of the International Neuropsychological Society, 24(10), 1073–1083. https://doi.org/10.1017/S1355617718000577

15. Li, Shue, F., Zhao, N., Shinohara, M., & Bu, G. (2020). APOE2: protective mechanism and therapeutic implications for Alzheimer's disease. Molecular Neurodegeneration, 15(1), 63–63. https://doi.org/10.1186/s13024-020-00413-4

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