SEX DIFFERENCES DETECTED IN THE POWER OF EEG SIGNALS FOLLOWING A MEMORY TASK IN MILD ALZHEIMER'S DISEASE PATIENTS AND HEALTHY ELDERLY INDIVIDUALS

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ABSTRACT

Understanding sex differences in the use of task-related neural compensatory mechanisms in healthy elderly individuals and Alzheimer's disease patients is necessary to improve early diagnosis and staging of the disease. Measuring participants' brain activity at different frequencies with electroencephalography (EEG) in a resting state following a cognitive task might be a suitable measure to identify such differences, with early EEG-based biological signs (biomarkers). The present secondary data analysis investigated sex differences among healthy older adults and Alzheimer's disease patients in the power of EEG signals at the alpha (8-13 Hz) and theta (6-8 Hz) frequency bands, using the alpha/theta ratio (TAR), with alpha divided into sub-bands: alpha1 (8-10 Hz) and alpha2 (10-13 Hz). Data was obtained from EEG signals with eyes open, sampled from the end of each trial of a cross-modal memory task. Participants (73 mild Alzheimer's disease patients and 63 age-matched healthy controls) were repeatedly presented with a paired associated visual (image) and auditory (spoken word) stimulus and asked to make an Old and New decision for each stimulus pair. Compared with males, both healthy females and female patients showed higher post-task alpha1/theta ratio power. Moreover, patients were characterized by greater post-task alpha2/theta ratio power than healthy elderly adults. These results suggest that the benefits of female brain plasticity begin to deteriorate in females with mild Alzheimer's disease and supports suggestions that Alzheimer's disease patients recruit alternative neural processes to aid the completion of a task. It is hoped that future clinical trials account for such sex- and disease-related neural abnormalities, and that this will help the stratification of Alzheimer's disease patients, early diagnosis, and monitoring of the disease.

INTRODUCTION

Alzheimer's disease is the most prevalent of all neurodegenerative disorders worldwide. Without any definite treatment, Alzheimer's disease affects an individual's social, emotional, behavioural and cognitive functioning, such as memory, language and visuo-spatial orientation (Ippati et al., 2021). Recognising early biological or genetic signs of the disease (biomarkers) may help with early diagnosis and to differentiate between healthy aging, mild cognitive impairment (MCI) and Alzheimer's disease. MCI is a preclinical stage of Alzheimer's disease, often with subjective memory complaints and early pathological changes in the brain (Khazee et al., 2017). A recent framework suggested that clusters of dead nerve cells in the brain forming either plaques (β-amyloid) or tangles (tau tangles) of damaging proteins are the most reliable biomarkers providing sufficient basis for the diagnosis of Alzheimer's disease, even before the onset of cognitive decline (Glymour et al., 2018). However, these biomarkers involve the use of neuroimaging methods which have been often criticised for their high cost and invasiveness. (Rosenberg and Hillis, 2009). Additionally, growing evidence shows insufficient sensitivity of imaging techniques to detect pathology in its early stages (Murray, 2012).

EEG (electroencephalogram), specifically resting-state EEG (rsEEG), may offer an alternative approach as it is less expensive, and easier for the participant (Blinowska et al., 2017). rsEEG is a measure of the spontaneous brain activity, quantified as the strength of power at different frequencies in a state of relaxed vigilance with the eyes closed or open. Slower frequencies, such as theta (4-8 Hz) and delta (1-4 Hz), are involved in memory formation, navigation, and relaxation, whereas alpha frequency (8-12 Hz) is involved in perception, attention, and recognition (Klimesch, 1999). In Alzheimer's disease, significant power increases have been observed on the theta and delta frequencies, and decreases on the alpha frequency, when compared to healthy elderly controls (Meghdadi et al., 2021). Such shift from high-frequency towards low-frequency power is proportional to the stage and severity of the disease (Cassani et al., 2018).

Most rsEEG studies have used the absolute power of each frequency (Meghdadi et al., 2021; Babiloni et al., 2021; Scally et al., 2018), although Schmidt et al. (2013) suggested using the alpha/theta ratio (TAR) instead, because the power of each frequency may differ between individuals. TAR has been considered an advantageous measure of rsEEG in Alzheimer's disease patients, with an accuracy rate of 84% when discriminating between early stages of Alzheimer's disease and healthy individuals (Schmidt et al., 2013). In a study performed by Ozbek et al. (2021), participants with Alzheimer's disease had significantly lower alpha/theta ratio than healthy elderly adults.

Despite some advantages, Gunther et al. (1993) have criticised the insufficient sensitivity of rsEEG to detect functional abnormalities and neural compensatory processes in the early stages of Alzheimer's disease. Instead, they proposed using post-task rsEEG, which they found to be more sensitive to the disease-related neuropathological processes in the pre-clinical stage and thus more helpful in differentiating between healthy elderly individuals, MCI, and Alzheimer's disease. Previous research has found EEG alpha power differences between MCI individuals and healthy controls during a memory task, while no such differences were detected during the resting condition (van der Hiele et al., 2007).

Episodic memory, which is responsible for encoding and retrieval of personal experiences, is typically the earliest and most substantially impaired cognitive function in Alzheimer's disease (Tromp et al., 2015). Episodic memory is often tested in Alzheimer's disease patients using a combination of visual and auditory (cross-modal) memory task based on recognition memory: judging whether a visual or auditory stimulus has

previously been experienced (Old item) or whether a New item is presented (Rugg and Curran, 2007). Alzheimer's disease patients and most MCI patients perform worse than healthy older adults on this task, which has been associated with the reduced Old/New effect, manifested in reduced difference in ERP (event-related potential) waveforms measured by EEG (Waninger et al., 2018). In other words, healthy older adults show higher brain activity when the Old items are presented than the New items as they retrieve information from memory. In Alzheimer's disease patients, such difference in brain activity between the two conditions is reduced, as well as their memory performance.

Using rsEEG measures following a memory task may reveal important information about the compensatory processes used by Alzheimer's disease patients. Han et al. (2017) found that Alzheimer's disease patients display higher power of the alpha frequency than healthy controls while performing a memory task, both during encoding and retrieval of information. Han et al. (2017) suggested that patients recruit alternative neural structures when encoding information to meet the increased cognitive demands, and to compensate for the brain pathology, therefore requiring higher alpha activity.

These processes are most evident in the theta band (6-8 Hz), reflecting encoding of new information in the episodic memory, as well as the alpha band divided into sub-bands (alpha1 and alpha2). The low-frequency alpha1 (8-10 Hz) is responsible for one's global awake state and task-related attention (Chavanon et al., 2007). The high-frequency alpha2 (10-13 Hz) is involved in encoding and retrieval of semantic information from memory, and is therefore relevant when investigating memory-related EEG measures (Klimesch, 1999). For instance, Hidasi et al. (2007) found that Alzheimer's disease patients showed increased EEG power of the high-frequency alpha power following a memory task involving information retrieval. Conversely, a slight decrease in high-frequency alpha power was observed in healthy controls.

Sex Differences in Alzheimer's Disease

Female sex is a major risk factor for Alzheimer's disease: studies show higher prevalence of Alzheimer's disease in females, as well as worse signs of brain deterioration than males (Oveisgharan et al., 2018). However, these studies usually include patients diagnosed with Alzheimer's disease at later stages, omitting the sex differences in progression towards the diagnosis. In fact, the healthy female brain is better protected against deterioration due to the neuroprotective function of estrogen hormones acting as antioxidants for neurons (Behl and Manthey, 2000). Compared to males, females also have larger volume of several brain areas, mainly the hippocampus, which is responsible for learning and memory formation, cognitive functions usually affected by Alzheimer's disease (Kiraly et al., 2016). This is accompanied by greater rsEEG power across all frequency bands (Cave and Barry, 2021). However, beyond a certain point this neuroprotection may be counterproductive: Koenig et al. (2020) suggested that excessive brain plasticity and lack of oestrogen in older age often leads to the rise in neurotoxic by-products that may accelerate neurodegeneration.

These findings may explain the sex differences in progression from MCI to Alzheimer's disease: Females with MCI perform better at verbal memory tasks and show slower cognitive decline despite similar or worse hippocampal atrophy than males (Sunderman et al., 2016). Moreover, when examining the ERP amplitudes, females (both healthy and with clinical deficits) elicit larger Old/New effect than males (Guillem et al., 2009). This can be explained by greater female brain plasticity and neural compensation compared to males. However, the opposite is seen among patients diagnosed with Alzheimer's disease. Women diagnosed with Alzheimer's disease have higher levels of neuropathology which are also associated with worse clinical manifestations (mainly memory performance) of dementia than men (Barnes et al., 2005).

Research focusing on sex differences in rsEEG signals in Alzheimer's disease patients is limited. A recent study by Babiloni et al. (2021) found greater rsEEG alpha power in healthy females than males. Similarly, greater alpha frequency was found in females with mild Alzheimer's disease than males. In fact, rsEEG measures of healthy and patient females did not differ, suggesting greater neuroplasticity in females with mild Alzheimer's disease. Nevertheless, no studies to date have investigated such differences using post-task rsEEG and/or using alpha/theta ratio as a proposed standardised biomarker for Alzheimer's disease (Schmidt et al., 2013).

Sex differences in post-task rsEEG have been investigated in healthy older adults. Mathewson et al. (2015) found substantial alpha power increases in older women, whereas older men showed only negligible increase and more variable changes in alpha power following a memory task. These findings suggest that post-task alpha power in older women reflects higher brain plasticity, as well as 'state-like' processes. In other words, females are more likely to use neural compensatory processes than males, depending on their cognitive ability, task demands and life span difference (Volf and Provodnova, 2018).

The current project addresses the gaps in literature by investigating sex differences in post-task rsEEG with eyes open among Alzheimer's disease patients and healthy older adults. Current diagnostic criteria mainly focus on neuropathology as opposed to EEG signals, although rsEEG, especially following a memory task, has been shown to be an effective indicator of functional abnormalities in MCI and Alzheimer's disease (Hidasi et al., 2007; Meghdadi et al., 2021). This project investigated rsEEG signals sampled from the end of each trial in a cross-modal memory task including two conditions (New and Old), providing insight into task-related cognitive effort among Alzheimer's disease patients. Based on studies showing higher task-related alpha power among patients, compared to healthy controls (Hidasi et al., 2007), it was expected that Alzheimer's disease patients would be characterized by greater post-task rsEEG spectral power of TAR than healthy older adults.

Moreover, subjects' sex has been mostly considered in either healthy older adults or patients in advanced stages of the disease. One study found higher rsEEG alpha power in females with mild Alzheimer's disease (Babiloni et al., 2021). However, this study did not focus on post-task rsEEG. For this reason, early-stage (mild) Alzheimer's disease patients were included in this study. Based on previous research, it was hypothesised that there would be sex differences in rsEEG signals following a memory task with two conditions (New and Old) among healthy older adults and mild Alzheimer's disease patients. It was expected that healthy females would show higher power of TAR than healthy males. Similarly, it was expected that females with Alzheimer's disease would show higher power of TAR than males with Alzheimer's disease.

Knowing the effect of sex on post-task rsEEG in Alzheimer's disease may help to recognize the patterns of task-related neural compensatory mechanisms in females with mild Alzheimer's disease, and how these differ from healthy older females. It is vital to understand possible sex differences in the expression and progression of the disease, as this will help with early diagnosis and stratification of Alzheimer's disease patients. Specifically, increased TAR power in healthy females would signify better use of cognitive reserve leading to better cognitive performance than men. On the other hand, in females in the early stages of the disease, such patterns of rsEEG power increases would initially enable masking of the cognitive

symptoms, but later become insufficient to support cognitive performance (Babiloni et al., 2021). In the later stages of the disease, decreases in rsEEG power in females would be accompanied with rapid deterioration of clinical symptoms, and underlying brain pathology (Barnes et al., 2005).

Additionally, the research and development of standardised EEG-based biomarkers, such as the alpha/theta ratio, can lead towards better diagnostic tools which are urgently needed to detect the disease before the tissue loss or behavioural symptoms appear. This can improve clinical outcomes and support development of more effective treatments. For instance, Cassani et al. (2018) suggested that due to its non-invasiveness and low cost, rsEEG could potentially be used in outpatient settings to increase monitoring of the progression of the disease.

METHOD

Participants

A secondary retrospective data analysis was conducted, using data collected by Tieges et al. (2018). Patients with mild Alzheimer's disease in the primary study were recruited in 2010 from four specialist Memory Clinics: Cognatec Research Centre Memory Clinic (Blackpool), Bradford Memory Clinic (Bradford), Memory Assessment Research Centre (Southampton), and Glasgow Memory Clinic (Clydebank), based on following inclusion criteria: (a) primary subjective memory impairment complaints, (b) meeting the NINCDS-ADRA criteria for a diagnosis of possible Alzheimer's disease (McKhann et al., 1984), (c) no current pharmacological treatment for Alzheimer's disease or dementia, (d) scoring 20 or above on the Mini-Mental State Exam (MMSE), (e) ≥ 65 years, (f) being a native English speaker, (g) normal or corrected-to-normal vision and hearing.

Table 1 shows demographic information of the final sample including 63 participants in the Alzheimer's disease group (32 men), with mean age of 76.7 years with standard deviation (SD) of 6.23 years, and 73 age-matched healthy controls (HC) (36 men), with mean age of 73.3 years (SD = 5.92), recruited from the community. Mean MMSE score for patients was 23.7 (SD = 2.65), and 28.7 (SD = 1.64) for controls.

Table 1: Demographic characteristics of participants. Mean values (M) and standard deviations (SD) of demographic and clinical data. Sex F = females; Sex M = males; N = number of participants; % = percentage of participants; MMSE = Mini-Mental State Exam; GDS = Geriatric Depression Scale; Gdet = Global Deterioration Scale.

	Controls		AD patients	
Variable	M	SD	M	SD
Sex F (N, %)	37 (51%)		31 (49%)	
Sex M (N, %)	36 (49%)		32 (51%)	
Age	73.3	5.92	76.7	6.23
MMSE	23.7	2.65	28.7	1.63
GDS	2.6	2.82	5.1	3.27
Gdet	1.31	0.47	2.86	0.39

Materials/Stimuli

Cross-Modal Associative Memory Test

The Alzheimer's Disease Evoked Potential Test (ADEPT) consisted of associatively related pairs of simultaneously presented stimuli (picture and spoken word), for example an image of a train and the spoken word 'tunnel'. The written norms of words were used instead of spoken word norms to ensure adequate control across all stimuli used in the original study (Tieges et al., 2018).

Neuropsychological Measures

Participants completed the Mini-Mental State Exam (MMSE) (Molloy et al., 1997), which is a widely used, highly reliable measure of cognitive abilities for dementia patients, and a diagnostic tool for MCI. It is designed to measure memory, attention, calculation, orientation, language and visual construction (Sheehan, 2012). Furthermore, control measures such as the depression score assessed on the Geriatric Depression Scale (GDS) (Yesavage, 1988), and global deterioration score assessed on the Global Deterioration Scale (Gdet) (Reisberg et al., 1988) were administered to participants.

EEG Measures

The EEG signals were continuously recorded from a high-density sensor with 128 channels (electrodes) (Electrical Geodesics Inc., Eugene, Oregon; Tucker, 1993). The EEG signals were pre-processed in the Net Station software. Tieges et al. (2018) divided the EEG signals into segments (epochs), each containing one trial. Each epoch was composed of 3000 ms of the memory task (stimulus) and 1000 ms of post-stimulus resting-state EEG with eyes open. Epochs containing blink and eye movement artifacts, as well as electrodes measuring noisy signals, were removed before the analysis.

Procedure

Subjects were in a seated position, approximately 60 cm from a computer screen, on which the pictures were presented in colour on a black background. Studio speakers were used to present the spoken words.

The memory task lasted approximately 25 minutes. Some stimulus pairs were presented multiple times (two or three) after either short delay (6 items) or long delay (39 items). Participants were asked to judge whether they were presented with a new item that they saw for the first time or an old item that they had seen before. They did so by pressing a button labelled either "New" or "Old". The three conditions used in the original study were New (110 items), Old/Short (100 items) and Old/Long (60 items). For the purpose of this project (i.e., post-task resting state EEG power), two experimental conditions were used: "New" (identical to the original study) and "Old" (combination of Old/Short and Old/Long).

Subjects had to give their answer within each trial lasting 3 s, followed by 1 s of resting state with eyes open. Mean reaction times (RT) were determined, and memory performance measure (d') was calculated from the task scores as the difference between the number of correctly identified old items (hits) and old items incorrectly identified as new items (misses).

Table 2 summarises the behavioural results together with the overall ADEPT score combining brain signals in the form of ERP (event-related potentials) and the memory performance scores. Tieges et al., (2018) reported that Alzheimer's disease patients had significantly lower D' score than controls.

Table 2: Behavioural data from participants. Mean values (M) and standard deviations (SD) of behavioural data from the participants. AD patients = patients with Alzheimer's disease; D' = memory performance measure; ADEPT = ERP combined with behavioural measures.

	Controls		AD patients	
Variable	Males (M, SD)	Females (M, SD)	Males (M, SD)	Females (M, SD)
D'	4.11 (0.67)	4.2 (0.52)	2.76 (1.35)	2.26 (1.37)
ADEPT	-2.9 (2.21)	-2.12 (1.57)	0.86 (2.61)	1.74 (3.78)

Power Spectral Density Analysis

Power spectral density (PSD) analysis of post-task rsEEG epochs of individual subject data was conducted using the EEGLAB software (Delorme and Makeig, 2004) and MATLAB. Post-stimulus epochs of 1000 ms were extracted from the end of each trial. Only correct trials were included in the analysis to prevent the interference of confounding variables. Based on Ozbek et al. (2021), 18 channels were selected for the analysis and grouped together, based on electrode locations (frontal, central, temporal, parietal, occipital).

Next, the PSD of each frequency band (alpha, beta, gamma, theta, delta) was estimated for all epochs using the spectopo() function, averaging resulting values across the 18 channels. The absolute power of each frequency band was determined for each condition separately (New and Old). Subsequently, the alpha/theta ratio was calculated for each participant based on the power of alpha and theta.

Standard frequency bands have been defied as follows: delta (1-4 Hz), theta (4-8 Hz), alpha1 (8-10 Hz), alpha2 (10-13 Hz) and beta (13-30 Hz) (Babiloni et al., 2017). The alpha1 and alpha2 sub-bands were based upon previous research by Klimesch (1999) and Babilioni et al. (2021), as they reflect distinct cognitive processes.

Ethics

The ethics followed the BPS Code of Ethics and Conduct guidelines (British Psychological Society, 2018). The primary study by Tieges et al. (2018) was carried out in accordance with the Declaration of Helsinki (Revised; 2000).

Statistical Analysis

All data wrangling and analysis was done using R 9.0.351 (RStudio Team, 2021) with packages car (Fox and Weisberg, 2019), tidyverse (Wickham et al., 2019) and lsr (Navaro, 2015). This study examined whether there was a difference between (or an effect of) groups (Alzheimer's disease patients and healthy subjects) and sexes (males and females) as between-subject factors, and two conditions (New and Old) as a within-subjects factors on the power of alpha/theta ratio (TAR), calculated for each group and condition. The statistical test used to investigate such effects of the three variables was the analysis of variance: the three-way mixed-effects ANOVA, a type of statistical test which can be used to compare three or more variables.

In order to run the mixed ANOVA statistical test, it was necessary for the data to meet specific criteria. Namely, the population variances of the between-subject factors must be homogenous, the within-subject factor data must be normally distributed, and the sphericity assumption must be maintained, which means that variances of the differences between multiple levels of the variable must be homogenous. Additionally, data should not contain extreme outliers. Current dataset met or has been corrected for all the assumptions and extreme outliers of TAR power above 10V2/Hz (Schmidt et al., 2013) were removed from the analysis.

RESULTS

The three-way mixed ANOVA did not detect any significant differences using alpha/theta ratio. However, when dividing alpha into sub-bands (alpha1 and alpha2), PSD analysis revealed Sex differences in the power of alpha1/theta ratio, and

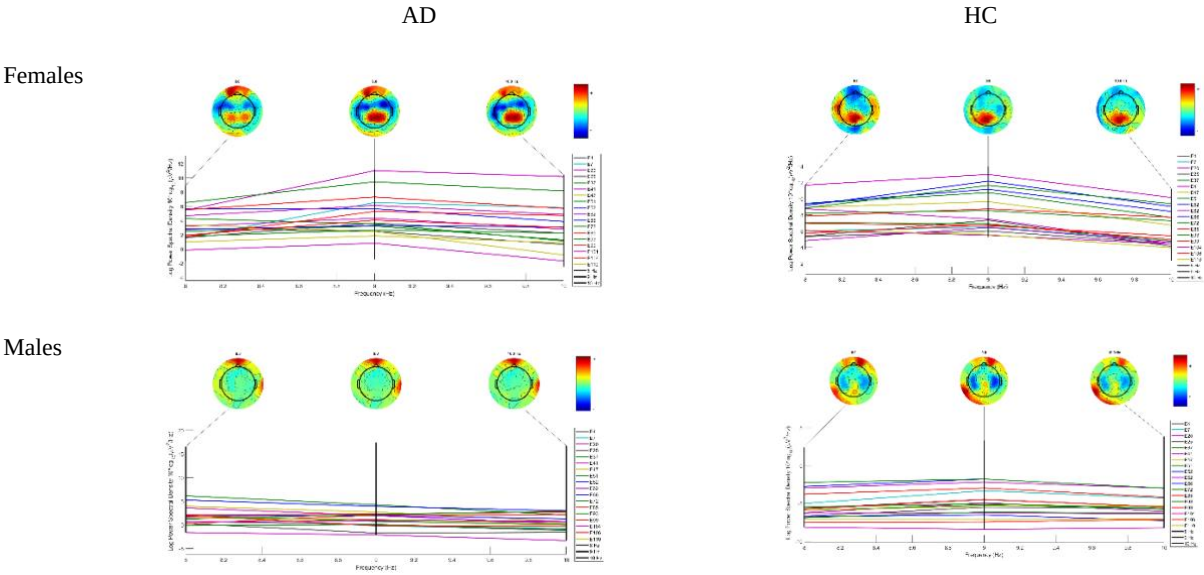

Figure 1: Single-Subject Plots of Power Spectral Density of Alpha1 During the "New" Condition, for patients with Alzheimer's disease (AD) and healthy controls (HC). Each line represents one of the 18 electrodes. Topographical scalp maps show the strength of PSD on the 8Hz, 9Hz and 10 Hz frequency. Red colour indicates the highest power.

Lower Alpha Band

The sex differences are demonstrated in Figure 1, showing single-subject plots of female and male healthy elderly controls (HC) and Alzheimer's disease patients' (AD) EEG power (PSD) of the alpha1 frequency band during the "New" condition. Individual subjects were selected randomly. Scalp maps indicated higher alpha1 power in both healthy and patient females, compared to males.

The three-way mixed ANOVA revealed a significant main effect of Sex for alpha1/theta ratio on the alpha significance level of 0.001. This means that the probability of falsely rejecting the correct null hypothesis was below 0.001 [$F(1, 126) = 10.68$, $p < .001$]. As shown in Figure 2, females have overall higher EEG power of TAR than males on the low-frequency alpha rhythms with medium effect size. Post-hoc pairwise comparisons showed that both healthy and patient females have significantly higher post-task alpha1/theta power ($p < .01$ and $p < .05$ respectively) than males. Furthermore, such effect was more significant within the "New" condition ($p < .001$) than the "Old" condition ($p < .05$). These results supported the hypothesis that females would show higher post-task rsEEG TAR power than males. This is likely to reflect greater involvement of neural compensatory processes among healthy females, which become insufficient in females with mild Alzheimer's disease.

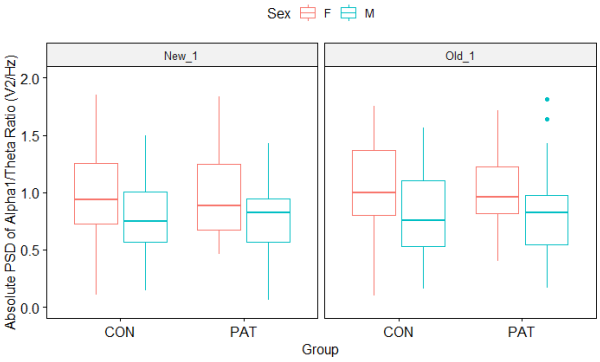

Figure 2: Distribution of Power Spectral Density of the Alpha1/Theta Ratio across groups. Healthy controls (CON) and patients with Alzheimer's disease (PAT). New_1 = alpha1/theta ratio within the "New" condition; Old_1 = alpha1/theta ratio within the "Old" condition.

Upper Alpha Band

Although there was no significant main effect of Sex, Condition or any significant interactions on the alpha2/theta ratio, the three-way mixed ANOVA revealed the main effect of group with Alzheimer's disease patients showing significantly higher post-task rsEEG TAR values than healthy controls on the high-frequency alpha rhythms [$F(1, 122) = 5.15$, $p < .05$]. Figure 3 shows the distribution of the results demonstrating higher alpha2/theta power in AD patients. Post-hoc comparisons showed the effect of Group on both conditions, slightly more significant within the "New" condition ($p = .019$) than the "Old" condition ($p = .05$). These results supported the hypothesised higher post-task EEG power of TAR among Alzheimer's disease patients than healthy older individuals, indicating higher cognitive effort invested in the memory task, and recruitment of alternative neural compensatory mechanisms in Alzheimer's disease.

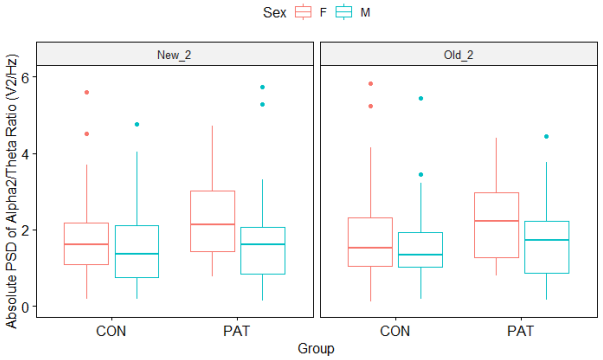

Figure 3: Distribution of Power Spectral Density of the Alpha2/Theta Ratio across groups. Healthy controls (CON) and patients with Alzheimer's disease (PAT). New_2 = alpha2/theta ratio within the "New" condition; Old_2 = alpha2/theta ratio within the "Old" condition.

DISCUSSION

The Effect of Sex

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It was hypothesised that both healthy elderly females and females with mild Alzheimer's disease would show higher post-task rsEEG absolute spectral TAR power than males. There was a significant effect of sex after dividing alpha into sub-bands (alpha1 and alpha2). Notably, both healthy and patient females showed significantly higher TAR values than males within the lower-frequency alpha1 (8-10 Hz). This result extends previous findings that healthy elderly females show substantially increased alpha power following a memory task compared to males (Mathewson et al., 2015). It also further extends the recent findings from Babiloni et al. (2021), who reported that healthy females and females with Alzheimer's disease showed higher alpha power of resting-state EEG than males on the lower individual alpha frequencies.

The results are only partially in agreement with previous studies that found significant power increases in the whole alpha frequency range among females (Mathewson et al. 2015; Volf and Privodnova, 2018). Although those studies examined power increases in relation to pre-task EEG measures, instead of solely using a post-task condition. Babiloni et al. (2021) argued that dividing alpha into sub-bands of alpha1 (8-10 Hz) and alpha2 (10-13 Hz) is essential as these reflect distinct cognitive processes. In the present cross-modal memory task, all participants had to engage their visual and auditory attention. Lower bands of the alpha frequency have been linked to the synchronization of neural connections involved in regulating one's global conscious state (Klimesh, 1999), as well as attentional demands of a cognitive task (Chavanon et al., 2007). In healthy subjects, alpha1 power is attenuated in relation to the strength of the cognitive load of a task (Gevins and Smith, 2000). Amplified power of the lower alpha band can usually be seen among older individuals as a compensatory neural mechanism to increase attention related to higher cognitive demands (Klimesh, 1999). This consolidates the present findings in that it suggests that older females, as opposed to males, use more neural compensatory processes to maintain attention to a cognitive task, irrespective of their clinical condition.

The effect of sex was more significant within the "New" condition than the "Old" condition. This is likely to reflect the increased cognitive demands of the "Old" condition among females with Alzheimer's disease, whose alpha1/theta power slightly decreased when the old items were presented.

Despite no significant effect of sex in the memory performance across patients and healthy controls, there were nonetheless remarkable non-significant sex differences in the mean d' scores among participants; healthy females performed slightly better than healthy males, whereas female patients performed slightly worse than male patients. Additionally, all healthy participants performed significantly better than patients (Tieges et al., 2018). Given that the power of alpha1/theta ratio was similar in females across both groups, it is plausible that these patterns of memory performance reflected more efficient use of cognitive reserve in healthy elderly females than females with Alzheimer's disease.

As known from previous research, healthy female brain is better protected against decline compared to males (Kiraly et al., 2016). The same neuroprotective factors can be seen among females with mild cognitive impairment (MCI) (Sunderman et al., 2016). However, these processes break when progressing towards clinical Alzheimer's disease. Present findings suggest that the benefits of female brain plasticity may already begin to diminish in females with mild Alzheimer's disease, with the increased rsEEG power of TAR becoming counter-productive and insufficient to support memory performance.

The Effect of Group

It was expected that the post-task absolute power of TAR would be higher among Alzheimer's disease patients than healthy elderly subjects. Compared to healthy controls, patients showed increased power of TAR when the alpha2 (10-13 Hz) was used.

These findings agree with previous studies that found power increases in the alpha2 frequency band among Alzheimer's disease patients during a memory task (Han et al., 2017), as well as when measured after the completion of a working memory task (Hidasi et al., 2007).

The present results indicating higher alpha2/theta ratio (greater alpha2 and lower theta power) in patients contradict the frequent finding that Alzheimer's disease patients show decreased alpha power and increased theta power during a resting-state EEG measure, compared to healthy controls (Meghdadi et al., 2021; Ozbek et al., 2021). However, the present study involved encoding new and retrieving old visual and auditory information from memory. Decrease in power of the upper alpha band (10-13 Hz) and increase in the theta band during a cognitive task in healthy individuals is thought to be involved in cortical activity and retrieval of semantic information from long-term memory (Klimesch, 1999). Specifically, Harmony et al. (1999) found that decrease at the parietal 12.45 Hz frequency power reflects the retrieval processes from long-term memory.

However, the response of neural networks involved in memory task performance in individuals with Alzheimer's disease usually differs from healthy elderly controls, resulting in greater EEG power values of the alpha2 band and reduced theta power (Ranchet et al., 2017). This is thought to reflect increased attempts to use compensatory neural mechanisms both during and after the completion of a task (Fonseca et al., 2011; Han et al., 2017; Hidasi et al., 2007). Hidasi et al. (2007) argued that these mechanisms are active in MCI and Alzheimer's disease of mild degree, in order to maintain cognitive functioning. However, there is a threshold where the compensatory resources become insufficient, leading to decline in cognitive performance (Ranchet et al., 2017). This can be seen among mild Alzheimer's disease patients in this study as they performed significantly worse on the task than healthy elderly adults, despite allocating higher amounts of cognitive resources to the task.

The difference in alpha2/theta ratio power between patients and healthy controls was more significant within the "New" condition than the "Old" condition. This is likely to be explained by the difference in ERP amplitudes. In the primary study, Tieges et al. (2018) found increased Old/New ERP amplitude effect among healthy elderly individuals, while such effect was absent among participants with Alzheimer's disease. Patients showed higher alpha2/theta power than healthy controls, which did not differ significantly across the two conditions. This suggests that Alzheimer's disease patients invested more overall cognitive effort in the task, irrespective of the condition, resulting in poorer performance on the Old/New judgment task.

Limitations

Due to the nature of the study (secondary data analysis), the EEG measures were collected for a different purpose. Tieges et al. (2018) investigated Old/New effects based on ERP amplitudes, therefore EEG was measured primarily during each trial of the cross-modal memory task. Participants were instructed to proceed with the task, although they were not instructed to rest after each trial.

Additionally, post-task EEG data acquisition usually involves comparison with the spontaneous resting-state EEG preceding the task (Hidasi et al., 2007; Mathewson et al., 2015; Volf and Privodnova, 2018). Considering that only post-task measures were available for this study, the TAR power could not be compared to baseline resting-state measures. Therefore, task-related functional changes in EEG signals could not be fully assessed.

The epochs containing rsEEG measures at the end of each trial were short, lasting only 1 sec before the next trial began. Other studies used a post-task resting state EEG recording lasting 2-3 minutes from which epochs were extracted (Hidasi et al., 2007; Kavcic et al., 2021). Cassani et al. (2018) reported that the standard epoch length in studies investigating rsEEG in Alzheimer's disease patients is 2 seconds.

Furthermore, the EEG data was acquired within a single testing session. This prevents the investigation of long-term effect of sex on the rsEEG power of TAR among Alzheimer's disease patients and healthy elderly subjects. Babiloni et al. (2021) emphasise the importance of such longitudinal evaluation in order to understand how sex affects EEG rhythms as the disease progresses.

Implications and Future Directions

Evidence from the present findings supports previous suggestions that post-task rsEEG TAR power provides accurate information about Alzheimer's disease-related functional changes (Cassani et al., 2018). Additionally, it supports studies calling for standardised division of the alpha band into sub-bands—as these sub-bands convey information about distinct cognitive processes (Babiloni et al., 2021; Cassani et al., 2018; Klimesch, 1999)—and the use of the alpha/theta ratio instead of separate frequency bands (Schmidt et al., 2013).

Furthermore, the present findings may help to understand the role of sex in the use of cognitive reserve and compensatory mechanisms among healthy older adults and mild Alzheimer's disease patients. Namely, neural compensatory processes recruited by older females in order to meet higher attentional demands of a cognitive task, such as greater power of alpha1/theta ratio than males, become insufficient in females with mild Alzheimer's disease. Similarly, increased alpha2/theta ratio power in response to higher demands on

semantic memory becomes an insufficient compensatory mechanism among Alzheimer's disease patients (both females and males). The sex difference in neural compensation implies that the sex factor should be considered when designing diagnostic criteria for Alzheimer's disease and the clinical stratification of patients.

However, more research is needed to determine sex differences in progression across different stages of Alzheimer's disease. Ranchet et al. (2017) reported that the cognitive workload and use of compensatory processes increase with the progression in the severity of the disease. Therefore, future studies should investigate how these processes differ among females and males across healthy older individuals, mild cognitive impairment, mild and severe stages of Alzheimer's disease.

Furthermore, the sex differences in functional TAR power changes from baseline rsEEG to post-task condition among Alzheimer's disease patients remain unknown. As reported by Klimesch (1999), both alpha/theta power and alpha/theta reactivity are vital to explaining individual differences in cognitive performance. Hence, future studies investigating sex differences in TAR power among patients should compare pre- and post-task rsEEG measures.

CONCLUSION

In sum, the aim of the present study was to address sex-related differences in the power (PSD) of the alpha/theta ratio obtained from rsEEG measures, following a cross-modal memory task among Alzheimer's disease patients and older healthy adults. Results revealed higher power of alpha1/theta ratio in both healthy females and female patients, compared to males. Considering that Alzheimer's disease patients performed worse at the memory task than healthy controls, this indicates that healthy older females efficiently use the cognitive reserve resources to support their memory performance. However, the same patterns of EEG power were insufficient among females with mild Alzheimer's disease. Furthermore, patients showed greater alpha2/theta power than healthy controls, as a result of increased cognitive effort related to encoding and retrieval of semantic information. Such increases did not differ among trial conditions (Old/New), leading to worse memory performance.

These results provide better understanding of the sex differences in the use of task-related neural compensatory mechanisms and suggest that these processes become insufficient among patients with mild Alzheimer's disease. This evidence may provide basis for consideration of the sex factor in the diagnostic stratification of Alzheimer's disease patients in the early stages of the disease. Together with neuropathological biomarkers and neuropsychological tests, standardised rsEEG biomarkers will be able to detect compensatory processes related to early brain pathology, which starts long before the onset of cognitive impairment, particularly among females. It is hoped that the diagnostic potential of EEG as a non-invasive, less expensive, and portable measure will be further researched in Alzheimer's disease patients, leading to its increased use in outpatient settings.

REFERENCES

Babiloni, C., Del Percio, C., Lopez, S., Di Gennaro, G., Quarato, P. P., Pavone, L., Morace, R., Soricelli, A., Noce, G., Esposito, V., Gallese, V., and Mirabella, G. (2017). "Frontal functional connectivity of electrocorticographic delta and theta rhythms during action execution versus action observation in humans." *Frontiers in Behavioral Neuroscience* **11**, pp. 20-20.

Babiloni, C., Noce, G., Ferri, R., Lizio, R., Lopez, S., Lorenzo, I., Tucci, F., Soricelli, A., Zurrón, M., Díaz, F., Nobili, F., Arnaldi, D., Famà, F., Buttinelli, C., Giubilei, F., Cipollini, V., Marizzoni, M., Güntekin, B., Yıldırım, E., and Del Percio, C. (2021). "Resting state alpha electroencephalographic rhythms are affected by sex in cognitively unimpaired seniors and patients with Alzheimer's disease and amnesic mild cognitive impairment: A retrospective and exploratory study". *Cerebral Cortex*.

Barnes, L. L., Wilson, R. S., Bienias, J. L., Schneider, J. A., Evans, D. A., and Bennett, D. A. (2005). "Sex differences in the clinical manifestations of Alzheimer disease pathology". *Archives of General Psychiatry* **62**(6), pp. 685-691.

Behl, C. and Manthey, D. (2000). "Neuroprotective activities of estrogen: An update", *Journal of Neurocytology* **29**(5-6), pp. 351-358.

Blinowska, K. J., Rakowski, F., Kaminski, M., De Vico Fallani, F., Del Percio, C., Lizio, R., and Babiloni, C. (2017). "Functional and effective brain connectivity for discrimination between Alzheimer's patients and healthy individuals: A study on resting state EEG rhythms". *Clinical Neurophysiology* **128**(4), pp. 667-680.

British Psychological Society. (2018). "Code of Ethics and Conduct (2018)".

Burke, S. L., Hu, T., Fava, N. M., Li, T., Rodriguez, M. J., Schuldiner, K. L., Burgess, A., and Laird, A. (2019). "Sex differences in the development of mild cognitive impairment and probable Alzheimer's disease as predicted by hippocampal volume or white matter hyperintensities". *Journal of Women & Aging*, **31**(2), pp. 140-164.

Cassani, R., Estarellas, M., San-Martin, R., Fraga, F. J., and Falk, T. H. (2018). "Systematic review on resting-state EEG for Alzheimer's disease diagnosis and progression assessment". *Disease Markers 2018*, pp. 5174815-26.

Cave, A. E., and Barry, R. J. (2021). "Sex differences in resting EEG in healthy young adults". *International Journal of Psychophysiology* **161**, pp. 35-43.

Chavanon, M., Wacker, J., Leue, A., and Stemmler, G. (2007). "Evidence for a dopaminergic link between working memory and agentic extraversion: An analysis of load-related changes in EEG alpha 1 activity". *Biological Psychology* **74**(1), pp. 46-59.

Choi, J., Ku, B., You, Y. G., Jo, M., Kwon, M., Choi, Y., Jung, S., Ryu, S., Park, E., Go, H., Kim, G., Cha, W., and Kim, J. U. (2019). "Resting-state prefrontal EEG biomarkers in correlation with MMSE scores in elderly individuals". *Scientific Reports* **9**(1), pp. 10468-15.

Delorme, A. and Makeig, S. (2004). "EEGLAB: an open-source toolbox for analysis of single-trial EEG dynamics". *Journal of Neuroscience Methods* **134**, pp. 9-21.

Fonseca, L. C., Tedrus, Gloria M. A. S, Fondello, M. A., Reis, I. N., and Fontoura, D. S. (2011). "EEG theta and alpha reactivity on opening the eyes in the diagnosis of Alzheimer's disease". *Clinical EEG and Neuroscience* **42**(3), pp. 185-189.

Fox, J., and Weisberg, S., (2019). “An {R} Companion to Applied Regression, Third Edition.” Thousand Oaks CA: Sage.

Gevins, A., and Smith, M. E. (2000). “Neurophysiological measures of working memory and individual differences in cognitive ability and cognitive style” *Cerebral Cortex* **10**(9), pp. 829-839.

Glymour, M. M., Brickman, A. M., Kivimaki, M., Mayeda, E. R., Chêne, G., Dufouil, C., and Manly, J. J. (2018). “Will biomarker-based diagnosis of Alzheimer’s disease maximize scientific progress? evaluating proposed diagnostic criteria”. *European Journal of Epidemiology* **33**(7), pp. 607-612.

Guillem, F., Mendrek, A., Lavoie, M. E., Pampoulova, T., and Stip, E. (2009). “Sex differences in memory processing in schizophrenia: An event-related potential (ERP) study”. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **33**(1), pp. 1-10.

Günther, W., Giunta, R., Klages, U., Haag, C., Steinberg, R., Satzger, W., Jonitz, L., and Engel, R. (1993). “Findings of electroencephalographic brain mapping in mild to moderate dementia of the Alzheimer type during resting, motor, and music-perception conditions”. *Psychiatry Res.* **50**(3), pp. 163–176.

Han, Y., Wang, K., Jia, J., Wu, W. (2017). “Changes of EEG spectra and functional connectivity during an object-location memory task in Alzheimer's disease”. *Frontiers in Behavioral Neuroscience* **11**, pp. 107-107.

Harmony, T., Fernández, T., Silva, J., Bosch, J., Valdés, P., Fernández-Bouzas, A., Galán, L., Aubert, E., and Rodríguez, D. (1999). “Do specific EEG frequencies indicate different processes during mental calculation?” *Neuroscience Letters* **266**(1), pp. 25-28.

Hidasi, Z., Czigler, B., Salacz, P., Csibri, É.,and Molnár, M. (2007). “Changes of EEG spectra and coherence following performance in a cognitive task in Alzheimer’s disease”. *International Journal of Psychophysiology* **65**(3), pp. 252-260.

Ippati, S., Ittner, L. M., and Ke, Y. D. (2021). “Sex differences in Alzheimer’s disease animal models”. *Sex and Gender Differences in Alzheimer's Disease*, pp. 3-22.

Király, A., Szabó, N., Tóth, E., Csete, G., Faragó, P., Kocsis, K., Must, A., Vécsei, L., and Kincses, Z. T. (2016). “Male brain ages faster: The age and gender dependence of subcortical volumes”. *Brain Imaging and Behavior* **10**(3), pp. 901-910.

Klimesch, W. (1999). “EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis”. *Elsevier B.V.*

Koenig, T., Smailovic, U., and Jelic, V. (2020). “Past, present and future EEG in the clinical workup of dementias”. *Psychiatry Research. Neuroimaging* **306**, pp. 111182.

Maestú, F., Campo, P., Del Río, D., Moratti, S., Gil-Gregorio, P., Fernández, A., Capilla, A., and Ortiz, T. (2008). “Increased biomagnetic activity in the ventral pathway in mild cognitive impairment”. *Clinical Neurophysiology* **119**(6), pp. 1320-1327.

Martín-Buro, M. C., Wimber, M., Henson, R. N., and Staresina, B. P. (2020). “Alpha rhythms reveal when and where item and associative memories are retrieved”. *The Journal of Neuroscience* **40**(12), pp. 2510-2518.

Mathewson, K. J., Hashemi, A., Sheng, B., Sekuler, A. B., Bennett, P. J., and Schmidt, L. A. (2015). “Regional electroencephalogram (EEG) alpha power and asymmetry in older adults: A study of short-term test-retest reliability”. *Frontiers in Aging Neuroscience* **7**, pp. 177-177.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., and Stadlan, E. M. (2011). “Clinical diagnosis of Alzheimer's disease: Report of the NINCDS--ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease”. *Neurology* **77**(4), pp. 333-333.

Meghdadi, A. H., Stevanović Karić, M., McConnell, M., Rupp, G., Richard, C., Hamilton, J., Salat, D., and Berka, C. (2021). “Resting state EEG biomarkers of cognitive decline associated with Alzheimer’s disease and mild cognitive impairment”. *PloS One* **16**(2), pp. e0244180-e0244180.

Molloy, D. W. and Standish, T. I. M. (1997). “A guide to the standardized mini-mental state examination”. *International Psychogeriatrics* **9**(S1), pp. 87-94.

Murray, A. D. (2012). “Imaging approaches for dementia”. *American Journal of Neuroradiology : AJNR* **33**(10), pp. 1836-1844.

Navarro, D. J. (2015). “Learning statistics with R: A tutorial for psychology students and other beginners.” (Version 0.6) University of New South Wales. Sydney, Australia. Available at: https://learningstatisticswithr.com

Oltra-Cucarella, J. J., Sánchez-San Segundo, M. M., Lipnicki, D. M., Sachdev, P.S., Crawford, J. D., Pérez-Vicente, J. A., Cabello-Rodríguez, L. L., and Ferrer-Cascales, R. R. (2018). “Using the base rate of low scores helps to identify progression from amnestic MCI to AD”. *Journal of the American Geriatrics Society (JAGS*) **66**(7), pp. 1360-1366.

Oveisgharan, S., Arvanitakis, Z., Yu, L., Farfel, J., Schneider, J. A., and Bennett, D. A. (2018). “Sex differences in Alzheimer’s disease and common neuropathologies of aging”. *Acta Neuropathologica* **136**(6), pp. 887-900.

Özbek, Y., Fide, E., and Yener, G. G. (2021). “Resting-state EEG alpha/theta power ratio discriminates early-onset Alzheimer’s disease from healthy controls”. *Clinical Neurophysiology* **132**(9), pp. 2019-2031.

Ranchet, M., Morgan, J. C., Akinwuntan, A. E., and Devos, H. (2017). “Cognitive workload across the spectrum of cognitive impairments: A systematic review of physiological measures”. *Neuroscience and Biobehavioral Reviews* **80**, pp. 516-537.

R Core Team (2021). “R: A language and environment for statistical computing.” [computer program] *R Foundation for Statistical Computing, Vienna, Austria.* Available at: https://www.R-project.org/.

Reisberg, B., Ferris, S. H., De Leon, M. J., and Crook, T. (1988). “Global deterioration scale (GDS)”. *Psychopharmacol Bull* **24**(4), pp. 661-663.

Rosenberg, P. B. and Hillis, A. E. (2009). “Biomarkers for Alzheimer’s disease: Ready for the next step.” *Brain* **132**(8), pp. 2002-2004.

Rugg, M. D. and Curran, T. (2007). “Event-related potentials and recognition memory”. *Trends in Cognitive Sciences* **11**(6), pp. 251-257.

Scally, B., Burke, M. R., Bunce, D., and Delvenne, J. (2018). “Resting-state EEG power and connectivity are associated with alpha peak frequency slowing in healthy aging”. *Neurobiology of Aging* **71**, pp. 149-155.

Schmidt, M. T., Kanda, P. A. M., Basile, L. F. H., da Silva Lopes, Helder Frederico, Baratho, R., Demario, J. L. C., Jorge, M. S., Nardi, A. E., Machado, S., Ianof, J. N., Nitrini, R., and Anghinah, R. (2013). “Index of alpha/theta ratio of the electroencephalogram: A new marker for Alzheimer’s disease”. *Frontiers in Aging Neuroscience* **5**, pp. 60-60.

Sheehan, B. (2012). “Assessment scales in dementia”. *Therapeutic Advances in Neurological Disorders* **5**(6), pp. 349-358.

Sundermann, E. E., Biegon, A., Rubin, L. H., Lipton, R. B., Mowrey, W., Landau, S., and Maki, P. M. (2016). “Alzheimer's Disease Neuroimaging Initiative, & For the Alzheimer's Disease Neuroimaging Initiative. Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. *Neurology* **86**(15), pp. 1368-1376.

Tieges, Z., Price, J., Hughes, A., McLean, G., Conway, B., and Kilborn, K. (Unpublished manuscript (2018)). *Event-related potentials from a cross-modal associative memory task as biomarkers of Alzheimer's disease*. University of Glasgow.

Toosizadeh, N., Ehsani, H., Wendel, C., Zamrini, E., Connor, K. O., and Mohler, J. (2019). Screening older adults for amnestic mild cognitive impairment and early-stage Alzheimer's disease using upper-extremity dual-tasking”. *Scientific Reports* **9**(1), pp. 10911-11.

Tromp, D., Dufour, A., Lithfous, S., Pebayle, T., and Després, O. (2015). “Episodic memory in normal aging and Alzheimer disease: Insights from imaging and behavioral studies”. *Ageing Research Reviews* **24**(B), 232-262.

Tucker, D. M. (1993). “Spatial sampling of head electrical fields: The geodesic sensor net”. *Electroencephalography and Clinical Neurophysiology* **87**(3), pp. 154-163.

Ullah, M. F., Ahmad, A., Bhat, S. H., Abu-Duhier, F. M., Barreto, G. E., and Ashraf, G. M. (2019). “Impact of sex differences and gender specificity on behavioral characteristics and pathophysiology of neurodegenerative disorders”. *Neuroscience and Biobehavioral Reviews*, **102**, pp. 95-105.

van der Hiele, K., Vein, A. A., Kramer, C. G. S., Reijntjes, R. H. A. M., van Buchem, M. A., Westendorp, R. G. J., Bollen, E. L. E. M., van Dijk, J. G., and Middelkoop, H. A. M. (2007). “Memory activation enhances EEG abnormality in mild cognitive impairment”. *Neurobiology of Aging*, **28**(1), pp. 85-90.

Volf, N. V., and Privodnova, E. Y. (2018). “Resting State EEG as an Indicator of Cognitive Training Effect in Older Adults”. *11th International Multiconference Bioinformatics of Genome Regulation and Structure/Systems Biology* **11**, pp. 117-119.

Waninger, S., Berka, C., Meghdadi, A., Karic, M. S., Stevens, K., Aguero, C., Sitnikova, T., Salat, D. H., and Verma, A. (2018). “Event-related potentials during sustained attention and memory tasks: Utility as biomarkers for mild cognitive impairment”. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* **10**(1), pp. 452-460.

Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L. D. A., François, R., Grolemund, G., Hayes, A., Henry, L., Hester, J. and Kuhn, M. (2019). “Welcome to the tidyverse”. *Journal of Open Source Software* **4**(43), pp. 1686.

Yesavage, J. A. (1988). “Geriatric depression scale”. *Psychopharmacol Bull* **24**(4), pp. 709-711.