Predictors of semantic and phonemic verbal fluency in patients with amnestic and multi-modal Mild Cognitive Impairment

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Date: 27/06/2020

Table of Contents

Abstract

Mild cognitive impairment (MCI) is a transitional stage between healthy aging and the onset of neurological problems commonly found in Alzheimer's disease (AD). The global growth of the population over the age of 65 and the related risk factors of old age in the development of AD are reasons to investigate the underlying mechanisms and early markers of cognitive deterioration. Using a sample from the Elizabeth TweeSteden memory clinic in Tilburg, a retrospective study including 147 patients with amnestic and multi-domain MCI, sex differences in semantic and phonemic verbal fluency were examined. These differences could be moderated by the influence of age, education, and type of MCI. Semantic and phonemic verbal fluency were assessed using the Groninger Intelligence Test (GIT-2) and the Frontal Assessment Battery (FAB) respectively. Education ($p<0.001$) and type of MCI ($p = 0.019$) were found to be statistically significant in predicting these scores. The results indicate that type of MCI and education are significant predictors of scores in verbal fluency. The findings are in line with the MCI literature which links multi-domain MCI as a risk factor for language impairments. The present thesis aimed to add relevant information to the ongoing research about possible predictors of and interventions for the progression from MCI to AD. The implementation of relevant variables in the assessment of MCI and subsequently AD could provide health care practitioners with reliable measurement tools for MCI in particular and thus improve the diagnostic process for cognitive deterioration in general.

Keywords: AD, FAB, GIT-2, language, MCI, sex differences, verbal fluency,

By the year 2050 it is estimated that there will be 2.1 billion elderly people living around the world (United Nations, 2017). Cognitive deterioration is common among people over the age of 65 including a decline in memory, attention, and language abilities that can lead to an altered sense of self, poor capacity for judgement, and the inability to care for oneself (Kukull, Higdon, et al. 2002). This set of symptoms is commonly summarized under the clinical syndrome of dementia including multiple types like vascular, frontotemporal with Lewy bodies, as well as dementia due to Parkinson's, Creutzfeldt-Jacob, and Alzheimer's disease (AD) (Buffington, Lipski, & Westfall, 2013). Not all elderly people develop dementia. However, the proportion of dementia in the general population aged 60 or higher is between five and eight percent which is equivalent to 50,666,198 people worldwide. This number is expected to increase to 82 million cases in 2030 and 152 million in the year 2050 (United Nations, 2020).

Dementia describes conditions that are both progressive and irreversible (Lezak, 2012). The Diagnostic and Statistical Manual Fifth Edition (DSM-V) replaced the term dementia with major and minor neurocognitive disorder. The new criteria comprising memory impairments now also include verbal abilities and language functioning as additional indicators of a neurocognitive disorder (APA, 2013). AD is the most common form of dementia affecting globally approximately 44 million people which is equal to 88% of the dementia population (Alzheimer's News Today, 2020). It is characterized by degenerative nerve cell changes within the cerebral cortex and a progressive global deterioration of cognition and personality (DeFina et al., 2013). Global cortical atrophy is seen in the progression of AD. Starting in the temporal lobes, the disease spreads across all regions of the brain. Frontal and temporal regions are especially important for language skills. Lesions located in these areas impair the appropriate use of words, the correct interpretation of sentences, and identification of non-verbal cues (Zamani et al., 2020; McKhann et al., 2011).

Language use includes among others auditory comprehension, visual perception, and the production of sounds. The assessment of language covers verbal fluency as a task measuring the ability to retrieve specific words within a limited time (Rosen, 1980). This ability relies on more than language functions but also on retrieval from memory, executive functions, selective attention, and inhibitory control (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Verbal fluency tasks commonly measure: 1) semantic (category) fluency, and 2) phonemic (letter) fluency (Thurstone & Thurstone, 1943; Lezak, 2012). In the former a person names words belonging to a certain category e.g. job-types or animals; in the latter the participant must name as many words beginning with a given letter, most commonly F, A, or S. Category fluency is associated with areas in the temporal lobes, whereas letter fluency is linked to frontal lobe regions (Haugrud, Lanting, & Crossley, 2010). Temporal regions include the superior temporal gyrus and Wernicke's area (language comprehension), the fusiform gyrus (object recognition) located in the ventral temporal lobe, and the auditory cortex (auditory information processing). Frontal areas include Broca's area (speech production) in the inferior frontal gyrus, and the primary and premotor cortex located in dorsal portion of the frontal lobes both of which are involved in the preparation and execution of movements related to speech (Baldo, Schwartz, Wilkins, & Dronkers, 2006). In a review of 58 word-production experiments, Indefrey and Levelt (2000) found language production to be related to left lateralized areas located within the perisylvian/thalamic network. Lesions in this network are associated with damage to the connection between Broca's and Wernicke's area. This may result in loss of the functional specialization for the processing stages of word production.

Language difficulties, for example problems with finding words, can be an early sign of cognitive decline (Petersen et al. 1999). Before the onset of severe cognitive problems, particularly memory or language deficits, milder forms of cognitive disabilities can be detected. An example of such a condition, affecting around 15-20% of people age 65 or older, is Mild Cognitive Impairment (MCI). It is defined as a transitional stage between healthy aging and the onset of AD (Petersen et al., 2004; Alzheimer's Association, 2020). The MAYO clinic subcategorized it into amnestic MCI memory-related issues and non-amnestic MCI (aMCI and non-aMCI) (Petersen et al., 2004; 2014). MCI can be unimodal, affecting only a single cognitive domain (sdMCI) or multi-domain (mdMCI), in which case there are several cognitive functions affected. Especially, multi-domain aMCI has been associated with higher progression rates to AD compared to single-domain aMCI (Petersen et al., 2014; Luo et al., 2018).

A study by Weakley, Schmitter-Edgecombe, and Anderson (2013) studied the influence of the type of MCI on verbal abilities with regard to category and letter fluency. Compared with healthy elderly controls, single domain aMCI patients showed no decrease in category or letter fluency. Patients with multi domain aMCI had lower total verbal fluency (category and letter) scores compared to the other groups. The authors concluded that verbal fluency decreases as more cognitive functions deteriorate over time. This conclusion is further supported by Pusswald et al. (2013) who investigated the prevalence of MCI subtypes in patients reporting cognitive impairments. The researchers used a sample of 676 memory clinic patients to establish the frequency of MCI subtypes (single-domain aMCI and multi-domain aMCI). MCI patients were subtyped as aMCI single domain (47 patients: 6.9%), aMCI multiple domain (57 patients: 8.5%), non-aMCI single domain (97 patients: 14.3%), and non-aMCI multiple domain (66 patients: 9.8%). The researchers concluded that the prevalence of MCI is substantially affected by the criteria used for its assessment. Single cognitive measures compared to a mean composite score for the level of impairment differed considerably, ranging from 39.5% to 84.3%. The study's findings were in line with previous frequency studies on MCI subtypes showing more prevalence for patients with md-aMCI and thus an increased risk for widespread cognitive deterioration beyond memory (Jungwirth et al., 2005; Fisher et al., 2007). Furthermore, a study by Steward, Bull, and Wadley (2019) found that patients with md-aMCI have greater impairment in their everyday functioning (e.g. listening, reading, or talking) compared to patients with sd-aMCI highlighting the importance of precise guidelines operationalizing MCI.

Mauri et al. (2012) investigated the progression rates from aMCI to dementia. Their sample included 208 individuals with aMCI who were followed over six years with a mean age of 73. AD was diagnosed in 93% of the converted cases with a progression rate of 80.7% within three years. A meta-analysis by Mitchel and Shiri-Feshki (2008) approximated the annual progression rate to be around five to ten percent. Although statistically significant, the two previous studies did not distinguish between single-/ or multi-domain aMCI which limits the implications for other cognitive domains. Another analysis found annual conversion probabilities ranging from eight percent to 36% depending on age, severity of AD, and differentiating between subtypes of MCI (Davis et al., 2018). This high range suggests that a clear cut-off for the onset of MCI can be challenging and is related to diagnostic criteria used in the assessment process.

The first diagnostic criteria for MCI were (1) subjective memory complaint supported by (2) objective impairment, (3) preserved general cognitive functioning, (4) normal activities of daily living, and (5) absence of dementia (Petersen et al. 1999). Later additional criteria included the possibility of cognitive impairment in domains beyond memory, such as executive functioning, visuospatial skills, and language (Petersen 2004; Winblad et al. 2004). A meta-analysis by Henry, Crawford, and Phillips (2004) found that deficits in verbal fluency can occur during the process of aging and often relate to cognitive deterioration in areas of language functioning. Multiple studies found that older participants typically produce fewer words than younger subjects during tests of verbal fluency (Bryan & Luszcz, 2000; Crossley, D'Arcy, & Rawson, 1997; Kavé, 2005; Lanting, Haugrud, & Crossley, 2009) suggesting a link between the participants' age and the decline in verbal abilities. Chêne and colleagues (2015) found that women have a higher risk of progressing to AD than men. Using the Kaplan-Meier estimator for lifetime data the researchers assessed the ten to fifty years risk estimates for AD of 7901 participants. Results suggested higher risk for females as compared to males of developing AD. The researchers attributed this difference to the relatively longer life expectancy of females compared to males (WHO, 2016). The overall lifetime risk of developing AD did not differ among females and males when assessment started at mid-life. However, the World Health Organization (2016) assessed the life expectancy in the Netherlands at age 60. The two groups do differ with females outliving males by a factor of 0.9 which is equivalent to 2.8 years on average. This highlights the significance of age as the number one risk factor for AD which is in line with previous research (Gurreiro & Bras, 2015). Further meta-analytic research suggests that the biological sex influences patterns of progression from MCI to AD with more females being affected by AD compared to males (Irvine, Laws, Gale & Kondel, 2012; Anderson, 2014). Anderson (2014) reported a higher prevalence of AD in women than in men connecting the difference to lifestyle related behaviors in men. These included, among others, unhealthy diets, higher alcohol consumption, and a more risk-related behavior overall. Lifestyle related behavior was associated with an increased risk of developing cardiovascular disease in middle age therefore potentially not surviving to develop any severe forms of AD. Other studies suggest that differences disappear or reverse with the onset of AD. Irvine et al. (2012) presented multiple reasons for this pattern including the decrease in the sex hormone estrogen in women of advanced age resulting in higher pathobiology, as well as genetic and brain-reserve related issues which impact the decrease in female verbal abilities with the onset of AD. The study's results showed that men with AD outperformed women particularly on verbal tasks.

This meta-analysis using 15 studies of AD patients also reported the overall cognitive functions to be more severely and widely affected in women as compared to men. It was theorized that this difference was a consequence of higher verbal abilities of females and therefore led to more obvious decline as compared to male patients. However, there is inconclusive evidence of differences in verbal abilities due to small sample sizes used in the study (Sato, 2020).

There are contradictory findings throughout the MCI/AD literature. Sex differences as an indicator of advantages in verbal fluency or an implication for different progression rates from MCI to AD is often unclear (Feretti et al., 2020). Hyde and Linn (1988) showed that women have a reliable advantage over men on verbal fluency across 165 studies. This meta-analysis, however, did not distinguish between letter and category fluency. Additionally, research by Laws, Duncan, and Gale (2010) found that studies with female AD patients reported a higher score of semantic verbal fluency as compared to males but did not report an accurate effect size measure. The researchers addressed the high disagreement in the literature regarding female advantages in verbal fluency over males which is supported by Wallentin (2009) who also recognizes the lack of clarity that exists on how sex differences influence the performance on verbal tasks. In comparison, a ten-year longitudinal study conducted by de Frias et al. (2006) including 600 nondemented patients aged 35-80 found stable sex differences with women outperforming men on verbal tasks especially semantic fluency.

Generally, there is high controversy within the MCI/AD literature regarding the effects of biological sex on language (Feretti et al., 2020; Laws et al., 2010; Wallentin, 2009). However, many studies have examined the progression of MCI and AD linked to sex differences (Artero et al., 2008; Bai et al., 2009; Chêne et al., 2015; Van den Heuvel et al., 2004). Artero et al. (2008) found this progression to be dependent on both age and education.

The researchers conducted a baseline, two, and four year follow up study of 6892 persons without dementia over the age of 65. Cognitive performance, clinical diagnosis of dementia, and environmental risk factors were evaluated at the three time points. Forty-two percent were classified with MCI at baseline. For both females and males, age and education were predictors of the progression from MCI to AD. This suggests a relationship between the variables age, education, and progression from MCI to dementia. The summarized studies and their findings, including a lack of clarity regarding the accurate assessment and operationalization of, and the influence from different variables on MCI, highlight the importance of further investigation in the context of language functioning. In particular, verbal fluency, type of MCI, and the moderating effects of age, sex, and education (Haugrud, Lanting & Crossley, 2010; Brucki & Rocha, 2004; Henry, Crawford & Phillips, 2004, Sundermann et al., 2019). Relatively few studies looked at the specific relationship between MCI, biological sex, and their influence on category and letter fluency scores while controlling for the effects of age, education, and type of MCI (Sundermann et al., 2016; McDonnell, Dill, Panos, & Amano, 2019).

The goal of this thesis is to explore whether there are sex differences in verbal fluency performance in patients diagnosed with MCI. The hypotheses are as follows:

(1) females with MCI will score lower than men with MCI on semantic verbal fluency,

(2) males with MCI will score lower on phonemic verbal fluency than females with MCI,

(3) older age will be predictive of lower total verbal fluency (category and letter) for both females and males,

(4) a higher-level education will be predictive of higher total verbal fluency for both sexes and,

(5) Type of MCI (sd-aMCI and md-aMCI) will be predictive of differences in verbal fluency.

Method

Participants

The original dataset of the Elizabeth-TweeSteden memory clinic in Tilburg, the Netherlands, included 188 MCI patients. Data collection started in October 2016 and concluded in January 2019. Inclusion criteria for participation in this retrospective study were female and male Dutch speaking aMCI/mdMCI patients and exclusion criteria were patients with different forms of dementia (e.g. vascular, AD), and/or other medical problems (e.g. tumors, thyroid dysfunction, cardiovascular problems). Of these patients, 147 individuals (75 males and 73 females) were included in the current study (see Figure 1). The ethical approval was given by the hospital's ethical committee in June 2016. In total 41 patients were excluded from the analyses due to either missing values or outliers in the variables relevant to this research. Values with three or more standard deviations for the FAB and the GIT-2 scores were considered outliers and excluded based on stem and leaf plots. For type of MCI only patients with either sd-aMCI or md-aMCI were included in the analyses and single-domain non-aMCI was excluded since it only contained three observations and was therefore considered statistically unfit.

Measures

Verbal fluency

Measures for the assessment of verbal (semantic and letter) fluency included the Frontal Assessment Battery (FAB; Dubois et al., 2000), and the Groninger Intelligence Test second version (GIT-2; Baredls, 2004).

The FAB letter fluency (F, A, S)

The Frontal Assessment Battery developed by Dubois et al. (2002) is a short screening test to evaluate executive functioning and discriminate between frontal dysexecutive phenotype and AD. The FAB has six subtests each scored 0-3 with a total maximum score of

18. An overall cut-off score of 12 on the FAB has a sensitivity of 77% and specificity of 87% in differentiating between frontal dysexecutive type dementias and AD. One subtest of the FAB assesses letter fluency (Chapados & Petridis 2009). The letter fluency subtest asks the participant to name as many words as possible beginning with a particular letter (F, A, and S) within 60 seconds. More than nine words results in a score of three, six to nine words score two, three to five score one and less than three words result in a score of zero (Slachevsky et al. 2004). The FAB test-retest reliability was found to be 0.78 (Dubois, Slachevsky, Litvan & Pillon, 2000). In the sample of the current study Cronbach's internal consistency of the FAB letter subtest was alpha = 0.91.

GIT2 category fluency (Animal, profession)

The Groninger Intelligence Test (GIT2) (Snijers & Verhage, 1964) is an assessment of intelligence. It includes, among others, measures of language abilities such as verbal (category) fluency. There are two parts measuring category fluency: (1) animals and (2) professions (60 seconds per category). The score is the number of correct answers (i.e. correct words belonging to that category (Barelds, 2004). Internal consistency was found to be Cronbach's alpha = 0.89 in the literature (Tellegen, 2005) and 0.94 in the current study.

Sociodemographic Variables: Age, education, and type of MCI

Age was assessed with a clinical interview and medical documentation. Education was assessed using the Verhage scale which is a 7-point scale with one through four being considered as low, five as middle, and six and seven as high education (Verhage, 1964). The Mayo criteria were used to define MCI in the present study (Petersen et al., 1999). The criteria include (1) the presence of a memory complaint, (2) impaired memory function for age group, (3) preserved general cognitive functioning, (4) intact activities of daily living (ADL), (5) and the absence of dementia.

Statistical analyses

Three t-tests were used to test for preliminary differences in age, education, and type of MCI between the two groups (females and males). Preliminary analyses including the Levene’s test (Levene & Howard, 1980) for the test of equal population variances, the Variance Inflation Factor (VIF; Daniel, 1960) for the issue of multicollinearity, and a scatter plot were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity within the sample.

Two multiple linear regression analyses, for each dependent variable (verbal fluency assessed by GIT-2 for category, and FAB for letter) were conducted including four blocks for sex as the independent variable, and age, education, and type of MCI as moderating variables. One MANCOVA was conducted in order to test for interaction effects between type of MCI, sex, and their influence on the two verbal fluency measures (FAB-letter and GIT-2 category) while controlling for the influences of age and education.

A two-sided alpha = 0.05 was used as a significance cut-off value for all statistical procedures and to control for multiple testing a Bonferroni correction was applied if needed. All statistical analyses were performed using SPSS version 26 for Macintosh OSX. A power analysis was conducted prior to the analyses using G*Power (Buchner, Erdfelder, Faul, & Lang, 2010). It revealed that for an effect size of d = 0.3, a total sample of 107 was needed. The final sample size in the present study was 147.

Results

Sociodemographic characteristics of the sample

Males and females were compared on the descriptive variables age, education, and type of MCI using t-tests. Age and education were found to be significantly different between males and females with females being on average older and less educated than males (t (145) = -2.257, p = 0.026; t (140) = 2.642, p = 0.009). For full information on the descriptive statistics see Table 1 (Appendix).

Multiple linear regression analyses

Hypotheses 1-5

To test letter fluency, sex, age, education, and type of MCI were divided into four blocks. Sex was included in block one of the analysis explaining 0.2% of the variance in letter fluency. Including education in block two 2.2% of the variance was explained by the model. After the inclusion of age, 4.4% of the variance in letter fluency was explained by sex, education, and age in block three. The final block including sex, age, education, and type of MCI explained 4.5%. The whole model was not statistically significant (F (4,146) = 1.682, p = 0.157). Information on the variables is summarized in Table 2.

For category fluency, four blocks including sex, age, education, and type of MCI were formed. Sex alone explained 1.1% of the variance in category fluency scores and was not statistically significant on its own. The second model including sex and age explained 2.3% of the variance found in the category fluency scores. With the inclusion of the variables sex, age, and education in model three the explained variance was 12.6%. After the inclusion of all four variables the final model explained 15.9%. Model four was found to be statistically significant (F (4, 146) = 6.733, p < 0.001) with education and type of MCI as the only two statistically significant predictors of differences in category fluency scores with beta values of

0.321 and -0,183 with p < 0.001 and p = 0.019 respectively (see Table 3). Table 4 shows the descriptive statistics of the related tests.

MANCOVA

The MANCOVA revealed no significant effect of either type of MCI or sex and revealed no interaction between the two variables for the scores of letter fluency assessed with the FAB subtest (F (5,141) = 1.383, p = 0.234). For category fluency assessed with the GIT-2 the MANCOVA showed a significant effect of education and type of MCI on category fluency scores (F (5,141) = 5.397, p<0.001) but no interaction effect between the variables sex and type of MCI. Education and type of MCI were the only significant predictors for scores on category fluency. Table 5 presents a summary of the MANCOVA and Figures 2-3 show further visualization of its results.

Discussion

This paper studied the effects of the biological sex on (1) letter fluency and (2) category fluency including the moderation by age, education, and type of MCI. It was predicted that females would score lower on letter fluency and males would score lower on category fluency (Hypotheses 1&2). These differences would be moderated by the effects of age, education, and type of MCI (Hypotheses 3-5). The analyses showed that there was no statistically significant effect of biological sex on either of the two verbal fluency measures. For letter fluency which was measured using the FAB-letter-subtest no regression model was found to be statistically significant. The fourth model for category fluency measured with the GIT-2 was the only significant model and showed effects of education and type of MCI on category fluency scores. The prediction that (1) females with MCI would score lower than men with MCI on semantic verbal fluency, and (2) that males with MCI would score lower on phonemic verbal fluency than females with MCI was rejected. Hypothesis 3, namely that older age would be predictive of lower total verbal fluency (category and letter) for both females and males, was also rejected. While age had an influence on the verbal fluency score for both letter and category fluency this influence did not reach statistical significance in any of the regression models nor the MANCOVA. Hypothesis (4) that a higher-level education would be predictive of higher total verbal fluency for both sexes was retained. The last hypothesis that type of MCI would be predictive of differences in verbal fluency scores was accepted. Although only two of the five original hypotheses were retained, the overall results of this paper are in line with the existing literature.

Multiple studies did not find significant differences in verbal abilities between females and males in the MCI population (Irvine, Laws, Gale, & Kondel, 2012; Wallentin, 2009). Studies investigating the effects of age and education found that both variables influence scores on verbal fluency (Kavé, 2005; Artero et al., 2008). No biological sex differences could be found in the present sample, yet several reasons could account for these results. First, the applied assessment tools (FAB and GIT-2) for letter and category fluency might lack sufficient reliability and are thus not sensitive enough to detect a significant difference. Internal consistency for the FAB and GIT-2 in general was found to be 0.78 and 0.89 respectively (Dubois, Slachevsky, Litvan, & Pillon, 2000; Tellegen, 2005). However, the corresponding subtests for FAB-letter and GIT-2 category verbal fluency might not have been extensive enough for an accurate assessment of the letter and category fluency. Second, verbal abilities are made up of language functions beyond letter and category fluency. Examples include verbal memory, selective attention, and executive control that need separate assessment to account for their individual influences (Zamani et al., 2020). The FAB is commonly used to detect impairments in executive functioning, which is linked to activation in the frontal lobes. Lesions in these areas can lead to impaired planning, loss of impulse control or emotional irritability, and decrease the ability to produce words with a given letter i.e. letter fluency (Haugrud, Lanting, & Crossley, 2010). The distinction between the impairment in executive function and the inability to retrieve words is inadequately reflected in the FAB as a whole. Therefore, the assessment with the FAB-letter subtest might not be extensive enough as a measure of letter fluency (Dubois, Slachevsky, Litvan, & Pillon, 2000).

Sex, age, and education have been related to verbal fluency and MCI in different studies throughout the literature (Irvine, Laws, Gale, & Kondel, 2012; Anderson, 2014; Artero et al. 2008; McDonnell, Dill, Panos, & Amano, 2019; Bryan & Luszcz, 2000). However, more variables could influence the relationship between sex, MCI, and verbal fluency. A study by Clark et al., (2013) found that lower scores of letter and category fluency were related to reduced grey matter density in the lower right temporal lobe, an area associated with semantic memory. Their results showed that levels of semantic memory impairment had a significant influence on the performance during the test for both phonemic and semantic verbal fluency. This suggests that a difference in cerebral atrophy could imply different accessibility of phonemic and semantic clusters found in the semantic memory. Another study by Mirandez et al., (2017) investigated which verbal fluency type is best distinguished between healthy elderly and MCI patients, and whether cerebral-spinal fluid (CSF) biomarker would correlate with these measures. Results showed that lower scores on category fluency alone were most effective in discriminating between healthy controls and MCI patients with a negative correlation to Tau levels in the CSF suggesting a link between biomarkers presence and category fluency. Inclusion of grey matter density measures and CSF biomarker (e.g. Tau proteins) availability could provide a more complete account of the potential cognitive deficits and improve clinical diagnosis.

The results in the present study support a common trend found in the literature on verbal fluency and MCI, but also AD, and language in general. In the literature no reliable differences could be found that would show a conclusive difference in verbal fluency abilities between females and males (Wallentin, 2009). The different development from MCI to AD between females and males, as discussed in Anderson (2014) and Irvine et al. (2012), might not solely be connected to differing verbal fluency and language abilities between these two groups but rather due to differences in life expectancy (Chêne et al., 2015). Moreover, AD is associated with far greater neuropathology than MCI so a decrease in verbal fluency that is not present during the transitional stage of MCI could become apparent once the neuropathology found in AD increases. The precise operationalization of MCI thus becomes relevant in the assessment of this transitional stage. Accurately locating where cerebral atrophy occurs and to what extent the progression can be measured by means of verbal fluency tasks in addition to imaging techniques (fMRI, PET, ERP) could become an important extension in clinical practice (Ardila & Bernal, 2016; Gernsbacher & Kaschak, 2002). Damage to the frontal and temporal lobes associated with a decrease in letter and category verbal fluency, respectively, might increase with the progression of nerve cell damage throughout the course of AD (Yeung et al., 2016; Scheff et al., 2011).

Limitations of the present study include the limited assessment of verbal fluency, i.e only incorporating two assessment tools and the fact that it was cross-sectional. Although the findings on differences between males and females in verbal abilities were found to be inconclusive, the overall measurement of language functioning in patients with MCI is considered a reliable tool for the assessment of potential neurological deficits due to a progressive neuropathological disease such as AD. Including an overall measure of verbal fluency, language production, understanding, and measures with greater sensitivity to letter and category fluency could account for more accurate assessment. In this context, the use of complete aphasia batteries e.g. the Arizona Battery for Communication Disorders of Dementia, the Sydney Language Battery, or the Addenbrooke's Cognitive Examination III could be beneficial in future research. These three aphasia batteries were found to be the most reliable tools with regard to standardization, normative data, and criterion validity in a review examining 18 commonly used aphasia batteries (Krein, Jeon, Amberber & Fethney, 2019). The complete aphasia battery approach is supported by Mueller et al. (2015) who tested for verbal fluency in early memory decline and highlighted the importance of multiple measure of verbal fluency for an accurate assessment of language functioning in middle aged adults at risk for AD. Another limitation of this study was that it was a retrospective, convenience sample drawn from one existing pool of patients. Therefore, an aphasia battery could not be used in this retrospective study. It could be interesting to draw random samples from multiple hospitals to increase the external validity of the results and to create an experiment in which different groups of MCI patients are compared on language abilities. At the moment it is difficult to generalize the findings and draw reliable conclusions. An increase in generalizability could be achieved by stratified random sampling from multiple MCI and AD health care institutions.

An experimental design could be an improved approach to distinguish among sex, type of MCI, age, and education groups and their language abilities. It could provide evidence of the specific effects of single variables like types of MCI beyond aMCI and mdMCI, education, and age on verbal fluency tasks. Using a double-blind randomized control group design in which patients would be assigned to different conditions with varying assessment tools i.e. different aphasia batteries would lead to higher reliability, generalizability and reduced experimenter effects. Each condition would represent either one language measure, two, or a complete aphasia battery. The groups would be assigned using balanced designs to control for symmetric carry-over effects.

Future research should focus on the inclusion of more reliable tools for the assessment of category and letter fluency with regard to construct validity and reliability. In particular the Frontal Behavioral, the Western Aphasia Battery, and the Addenbrooke's Cognitive Examination III were found to be the most relevant batteries in the area of language and executive functioning (Kertesz et al., 1979, 1982; Krein et al, 2019). Additionally, a bigger sample is advised since the exclusion of 40 patients in the current sample due to outliers could have affected the analyses and results. Different interactions and covariates that influenced the relationship between the biological sex and scores on verbal fluency need to be taken into account (Killin, Star, Shiue, & Russ, 2016; Katz et al., 2015; Sultana & Butterfield, 2009). Johannson et al. (2020) investigated associations between neuropsychiatric symptoms (i.e., apathy, anxiety, and depression) and cerebral atrophy. The researchers found apathy and anxiety to be predictive of cognitive decline and faster overall cognitive deterioration. Apathy was related to frontotemporal and subcortical atrophy. Frontotemporal regions have been linked to language and verbal fluency suggesting a link between negative emotionality and performance on verbal tasks (Zamani et al., 2020; McKhann et al., 2011). Another important theory that outlines the influences of cognitive performance in older adults is called the stereotype threat theory (STT). It states that the fear of fitting into a certain stereotype influences cognitive performance of older adults (Meisner, 2012). This is supported by Barber (2017) who suggests that motivational changes under stereotype threat are the main underlying mechanisms of stereotype effects in the elderly. In an experimental design these variables could be included as covariates to increase the power of the statistical analyses.

In the current study age and education were included as covariates. However, these variables do not correlate with specific regions in the brain mostly related to language functions but to larger networks throughout the brain. The ageing brain is associated with cerebral atrophy in all areas of the supratentorial regions i.e. all areas above the cerebellum

(Raji et al. 2009) and education is associated with networks and white matter tracts connecting various regions of the brain including the parietal, temporal, frontal lobes, and sub-cortical regions like the limbic system (Diamond, 2006; Gabriel, 2003; Groen, 2010; Lezak, 2012). Future research should carefully select covariates to prevent overlap in neurological activity between these variables and enable precise assessment of the level of cortical deterioration and related cognitive problems.

One strength of the current study was the statistical power of the analyses providing reliable results of the tests. The inclusion of type of MCI in the analysis and its interaction effect with sex led to more increase in statistical power. Even though the interaction effect was not statistically significant introducing type of MCI as a covariate led to an increase in statistical power since type of MCI turned out to be a significant predictor of differences in verbal fluency. Another strength was the measurement of internal consistency for the FAB letter subtest and the GIT-2 showing high reliability for both tests. Although an aphasia battery might provide a complete picture, Cronbach's alpha of 0.91 (FAB) and 0.94 (GIT-2) is considered very high (Nunally, 1978). However, as this study only made use of two assessment tools it could not provide the entire assessment of language beyond verbal fluency. Finally, the inclusion/exclusion criteria were clearly stated and summarized in a flowchart which provides a clear overview of the selection process in addition to the graphical representation of the MANCOVA results and thus helps identify possible variables that might be interesting in future research e.g. the inclusion of more subtypes of MCI (single-domain non-aMCI and multi-domain non-aMCI). Exploring causal links between the onset of language problems and their potential indication for the beginning of neurocognitive deterioration may help health care professionals to improve interventions by addressing these problems prior to an apparent negative impact on a person's subjective experience.

This thesis provided further support to the discussion on language impairment as an indicator of cognitive decline by contrasting existing literature with the influence of education and type of MCI on verbal fluency scores. It outlined the possible influences of sex, age, education, and type of MCI on verbal fluency types and analyzed possible interaction effects between sex and type of MCI. Future research might consider testing for interactions between education and type of MCI or possible three-way interactions which are beyond the scope of this thesis. The current elaboration on the existing MCI literature and support of general trends of language functioning is an important contribution to the clinical assessment within this population.

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Appendix

Tables

Table 1

Sociodemographic data from final sample

Variable	Females	Males	Mean	SD	p-value
	49% (N=72)	51% (N=75)			
Age	77.15	74.53	75.82	7.133	0.026*
Education	4.11	4.68	4.40	1.338	0.009*
Type MCI					0.521
a-MCI	44% (N= 15)	56% (N= 19)			
md-MCI	50.4% (N=57)	49.6% (N= 56)			

Note: * = $p < 0.05$

Table 2

Results Multiple Regression Analysis for FAB letter fluency

Model	Constant	beta	t(145)	p-value
1	2.272			
Sex		-.047	-.564	.573
2	1.925			
Sex		-.014	-.167	.867
Education		.153	1.822	.071
3	2.882			
Sex		.011	.130	.897
Education		.150	1.789	.076
Age		-.140	-1.688	.094
4	2.911			
Sex		.016	.143	.886
Education		.148	1.764	.080
Age		-.138	-1.645	.102
Type of MCI		-.039	-.474	.636

Note: $* = p < 0.05$

Table 3

Results Multiple Regression Analysis for GIT-2 category fluency

Model	Constant	beta	t(145)	p-value
1	29.498			
Sex		-.104	-1.263	.209
2	21.104			
Sex		-.034	-.419	.676
Education		.332	4.135	.000*
3	28.997			
Sex		-.015	-.186	.853
Education		.329	4.110	.000*
Age		-.103	-1.301	.195
4	30.520			
Sex		-.009	-.117	.907
Education		.321	4.076	.000*
Age		-.090	-1.148	.253
Type of MCI		-.183	-2.370	.019*

*Note: *=p<0.05*

Table 4

Results of the MANCOVA for GIT-2 and FAB with type of MCI and sex as IVs and age and education as covariates.

	Male		Female		*F*	*p*	*Partial etasq*
	M	*SD*	*M*	*SD*			
FAB letter	2.271	.649	2.211	.646	1.388	.234	.047
GIT-2 category	29.498	7.03	27.995	7.40	5.397	.001*	.161
Education-FAB	4.68	1.453	4.11	1.145	16.210	.001*	.103
Education-GIT2	4.68	1.453	4.11	1.145	2.972	.087	.021
Age-FAB	74.53	7.180	77.15	6.881	2.269	.134	.016
Age-GIT2	74.53	7.180	77.15	6.881	1.053	.306	.007
aMCI-FAB	2.241	.847	2.3788	.390	2.706	.001*	.039
mdMCI-FAB	2.277	.577	2.1672	.694			
aMCI-GIT2	31.222	8.435	31.839	8.016	35.511	.001*	.039
mdMCI-GIT2	28.9126	6.490	26.981	6.961			

Note: *=p<0.05

Figures

Figure 1

Flowchart of Exclusion and Inclusion criteria

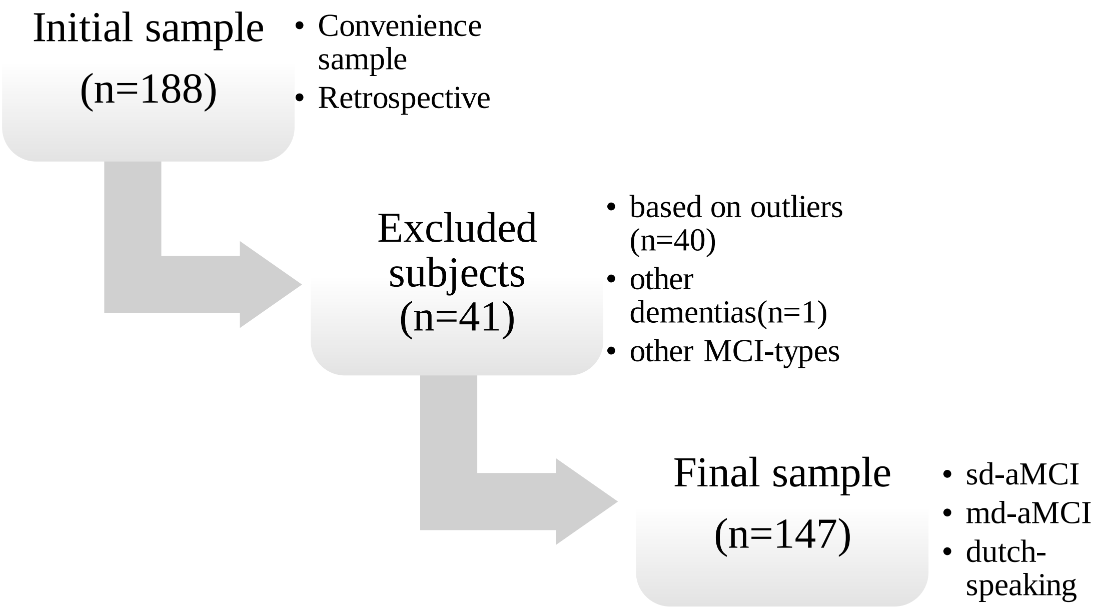

Figure 2

MANCOVA line-graph with adjusted means for letter fluency

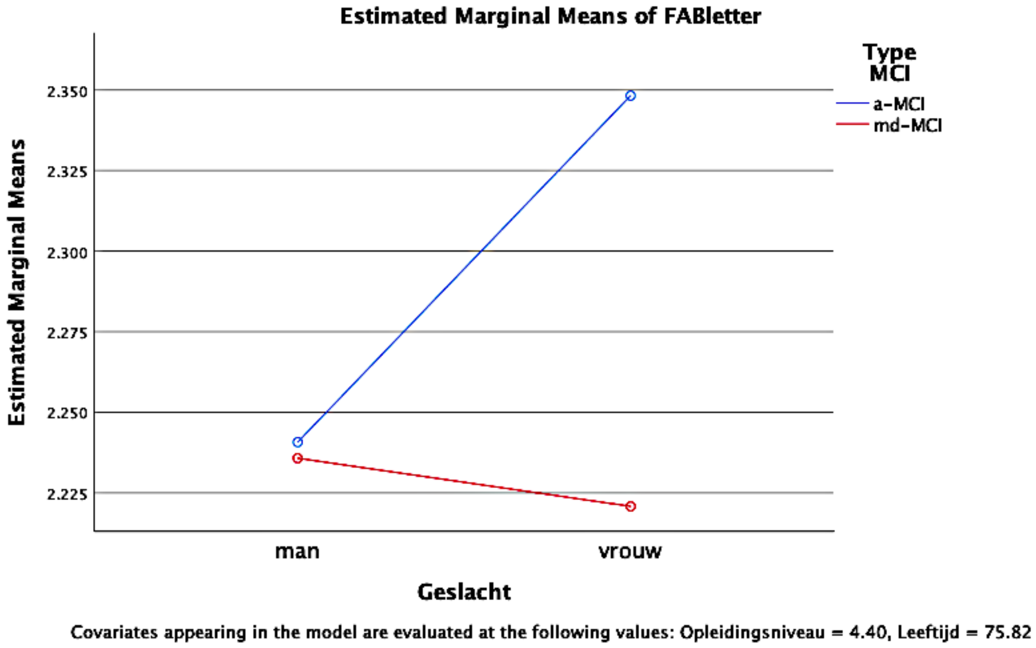

Figure 3

MANCOVA line-graph with adjusted means for category fluency