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The influence of first-degree family history on gray matter atrophy and cognitive performance in Alzheimer's disease: a clinical profile

Master thesis
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Abstract

Introduction Having a positive first-degree family history in dementia (FH+) is known to increase the risk of developing Alzheimer's disease (AD). Several studies show that healthy subjects with FH+ have a reduced gray matter volume (GMV) and cognitive performance compared to subjects with a negative family history in dementia (FH-). Furthermore, numerous studies show that subjects with a maternal family history (FHm) have more gray matter atrophy compared to subjects with a paternal family history (FHp) or FH-. However, knowledge about differences in GMV and cognitive performance between FH+ and FH- subjects, and specifically between FHm, FHp and FH- subjects, in AD patients is still scarce. Therefore, in this study we will investigate the influence of first-degree family history on gray matter atrophy and cognitive performance in AD patients.

Methods With the use of magnetic resonance imaging (MRI) and neuropsychological testing, we compared GMV and cognitive performance between FH+ and FH- patients, and specifically between FHm, FHp and FH- patients. In total, 123 FH+ patients (FHm = 67, FHp = 35) and 141 FH- patients were analyzed, looking at GMV in several regions of interest (ROI) and neuropsychological testing. To identify profiles of the different groups, we chose to use a control group that included participants with subjective cognitive complaints.

Results Our findings showed that AD patients with FH- had more gray matter atrophy in the left posterior temporal lobe compared to FH+ patients (uncorrected for multiple testing). Furthermore, comparisons between FHm, FHp, and FH- patients showed that FH- patients had more gray matter atrophy compared to FHm patients (uncorrected for multiple testing). Looking at the cognitive performance, FH- patients performed worse on executive functioning in comparison with FH+ patients. No differences were found between FHm, FHp and FH- patients. Lastly, no significant correlation was found between GMV and cognitive performance.

Discussion Findings in this study indicate that FH- patients are more affected than FH+ patients, which is not in line with previous literature. However, this study is one of the first studies to investigate in cognitively impaired patients and can be an interesting starting point for further research in this topic, since this could contribute to a better understanding of the effect of family history in AD patients.

Introduction

Due to population aging, dementia is considered a growing health problem in most countries worldwide (Ferri et al., 2005). According to the Dutch Central Bureau of Statistics (CBS), dementia is the main cause of death in the Netherlands, causing more than fifteen thousand deaths in 2016 (CBS, 2017). Dementia is defined as a progressive disorder caused by several neurodegenerative diseases, with Alzheimer's Disease (AD) as the most common cause of dementia (Hansen, Hughes, Routley, & Robinson, 2008; Prince et al., 2013). AD is characterized by atrophy in foremost the medial temporal lobe and precuneus (Thompson, et al., 2003), resulting in a progressive cognitive decline in memory, speech, behavior, and visuo-spatial perception (Chang & Silverman, 2004; Mosconi et al., 2010; Sonkusare, Kaul & Ramarao, 2005). Neuritic plaques and neurofibrillary tangles are typical pathological lesions in AD (Bondi et al., 2008; Chang & Silverman, 2004; Sonkusare, Kaul, & Ramarao, 2005), primarily affecting the medial temporal lobes in the beginning, eventually spreading to other regions in the temporal, parietal, and frontal lobes (Bondi et al., 2008, Chang & Silverman, 2004).

Several studies indicate that, aside from advanced age, genetic factors increase the risk of developing AD (Azad, Al Bugami, & Loy-English, 2007; Donix et al., 2010; Honea, Swerdlow, Vidoni, Burns, 2011; Mosconi et al., 2010; Scarabino, Gambina, Broggio, Pelliccia, & Corbo, 2016). Mutations of presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) genes are found in the rare, autosomal dominant forms of early-onset Alzheimer's Disease (EOAD) (Campion et al., 1999; Joshi, Ringman, Lee, Juarez, & Mendez, 2012). The e4 allele of the apolipoprotein E gene (APOE-4) is the most researched genetic factor associated with a higher risk in the much more common sporadic or late-onset Alzheimer's Disease (LOAD), and accounts for approximately 25% of the genetic risk (Heggeli et al., 2012). Yet, there is still much unknown about the remaining genetic factors in AD development (Ballard et al., 2011; Heggeli et al., 2012; Scarabino et al., 2016).

Literature shows that a positive first-degree family history (FH+), especially a parent, is an important risk factor in LOAD development (Bondi et al., 2008; Honea, Swerdlow, Vidoni, & Burns, 2011; Mosconi et al., 2007). Several studies found that cognitively normal individuals with FH+ have significantly more gray matter atrophy in AD-vulnerable regions, such as the posterior hippocampi and the precuneus,

compared to cognitively normal individuals without family history of AD (FH-) (Honea, Swerdlow, Vidoni, Goodwin, & Burns, 2010; Honea et al., 2011; Donix et al., 2010; Okonkwo et al., 2012). However, differences in family history of patients with cognitive impairments are still quite unknown (Ganske et al., 2016).

Interestingly, a couple of studies show that individuals with a maternal history of AD (FHm) seem to have an increased risk of developing the disease compared to individuals with a paternal (FHp), or no family history of AD (FH-) (Andrawis et al., 2012; Honea et al., 2010; Okonkwo et al., 2014). In the study by Honea et al. (2010), they tested cognitively healthy subjects with a family history of AD and found greater gray matter volume (GMV) reductions in the prefrontal cortices and the precuneus in subjects with FHm compared to FHp and FH- subjects. However, other studies could not replicate these results (Okonkwo et al., 2012; Wolters et al., 2017).

Next to imaging markers, cognitive performance in cognitively healthy groups based on family history is investigated in a number of studies (La Rue et al., 2008; Okonkwo et al., 2012; Wolf et al., 2005). A few studies found decreased cognitive performance, such as episodic memory dysfunction, in FHm subjects compared with FHp or FH- subjects (La rue et al., 2008; Wolf et al., 2005). Other studies did not find these results (Johnson et al., 2006; Okonkwo et al., 2012). As noted earlier, differences in gray matter atrophy between FH+ and FH- have been found (Honea et al., 2010; Honea et al., 2011; Donix et al., 2010; Okonkwo et al., 2012), which might lead to different patterns in cognitive performance. However, knowledge about possible differences in cognitive performance between FH+ subjects and FH- subjects, and specifically FHm subjects and FHp subjects, is limited. Furthermore, possible differences in cognitive performance in AD patients with first-degree family history is still unknown.

Therefore, in this study we will investigate the influence of first-degree family history on gray matter atrophy and cognitive performance in AD patients. Although several studies have investigated the influence of family history on GMV in cognitively healthy individuals (Honea, Swerdlow, Vidoni, Goodwin, & Burns, 2010; Honea et al., 2011; Donix et al., 2010; Okonkwo et al., 2012), the current study is the first study that investigated the combination of gray matter atrophy and cognitive performance in AD patients. This can contribute to a more thorough understanding of cognitive performances and imaging markers in AD, based on family history. Furthermore, the

database used in this study included patients from different parts of the Netherlands and possible results can be generalized to the Dutch population and perhaps other Western populations. When differences between FH+ and FH-, and FHm and FHp, are found, it could be of great importance in the improvement of the diagnostic process of AD.

There are several aims in this study:

1. Identify differences in gray matter atrophy in groups based on family history (FH+, FHm, FHp, FH-):

   Hypothesis 1a: More gray matter atrophy in ROIs in FH+ patients compared to FH- patients (e.g. medial temporal lobe, hippocampus, precuneus, posterior cingulate cortex, posterior temporal lobe, prefrontal cortex).

   Hypothesis 1b: More gray matter atrophy in ROIs in FHm patients compared to FHp and FH- patients (e.g. medial temporal lobe, hippocampus, precuneus, posterior cingulate cortex, posterior temporal lobe, prefrontal cortex).

2. Identify differences in cognitive performance in groups based on family history:

   Hypothesis 2a: Cognitive performance is lower in FH+ patients compared to FH- patients (e.g. episodic memory, verbal word fluency, semantic memory, and executive functioning).

   Hypothesis 2b: Cognitive performance is lower in FHm patients compared to FHp patients and FH- patients (e.g. episodic memory, verbal word fluency, semantic memory, and executive functioning).

3. Identify the relation between gray matter atrophy and cognitive performance in groups based on family history

   Hypothesis 3: Significant correlation between gray matter atrophy in ROIs and cognitive performance in groups based on family history.

Methods

Design

Data used in this study were obtained from a large database of the Dutch Parelsnoer Institute (PSI, http://parelsnoer.org). The Dutch Parelsnoer Institute (PSI) is

a collaboration of eight academic hospitals (UMC's) that collect clinical data and biomaterial from patients suffering from several chronic diseases (the so called "Pearls"). The Pearl Neurodegenerative Brain Diseases (NDZ) is a multi-center cohort study aiming to improve early diagnosis and predicting clinical decline or incident dementia in those who are not demented yet (Aalten et al., 2014). Patients were enrolled for the first time in March 2009 and are followed annually, resulting in a database of approximately 1000 cases.

Participants

From the PSI database 123 AD patients with a positive family history and 141 AD patients with a negative family history, aged between 47 and 92 years, were selected. Inclusion criteria of the NDZ at baseline were also applied in this study and previously described in Aalten et al. (2014). Furthermore, in this study inclusion criteria included patients who were diagnosed with AD at baseline (both possible and probable AD), and family history of first-degree relatives. Exclusion criteria included patients with Normal Pressure Hydrocephalus, Huntington's Disease, recent (<2 years) Transient Ischemic Attack (TIA) or Cerebrovascular Accident (CVA) or TIA/CVA followed by a cognitive decline within three months, history of psychiatric disorders (e.g., schizophrenia, bipolar disorder, psychotic symptoms), current major depressive disorder (DSM IV), cognitive problems due to alcohol abuse, brain tumor, epilepsy, and encephalitis. Additionally, patients who are incapacitated to decide for participation, patients without a reliable informant, or patients in which a follow-up assessment after one year was not possible were excluded. Lastly, we excluded patients who were diagnosed with AD at baseline but appeared to have another diagnosis in the follow-up. To identify profiles of the different groups, we chose to use a control group. This control group included participants with subjective cognitive complaints, using the same exclusion criteria.

Procedure

Data used in this study were collected at baseline according to Standard Operating Procedures (SOP's) of the PSI. The dataset consisted of clinical data, a cognitive assessment, MRI of the brain, blood samples and CSF samples. The methods of PSI NDZ have been described in detail previously (Aalten et al., 2014).

All procedures in the PSI study were approved by the Medical Ethics Review Committee of the VU University Medical Center. On site approval of the study were confirmed by the local Medical Ethical Committees. The research is performed in accordance with the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act. Furthermore, codes on 'good use' of clinical data and biological samples as developed by the Dutch Federation of Medical Scientific Societies were met. Written informed consent were obtained from all patients (Aalten et al., 2014).

Measures

Clinical data

Demographic data (e.g., age, gender, educational level, ethnicity, and marital status), medical and family history, and medication use were obtained at baseline through a semi-structured interview (Aalten et al., 2014).

Diagnosis

The diagnosis of dementia was made during the multidisciplinary meeting, based on test results and DSM-IV criteria (APA., 1994, as described in Aalten et al., 2014). Criteria for the diagnosis of AD were made according to NINCDS-ADRDA criteria guidelines (McKhann et al., 2011, as described in Aalten et al., 2014).

Family history

We defined a positive family history as a diagnosis of dementia and/or parkinsonism. Furthermore, the number of first and second-degree relatives, with specification of the relatives, and their age at time of diagnosis were identified (Aalten et al., 2014). To verify the diagnosis of AD, we obtained medical records of family members (including neuropathological reports when available). A positive family history (FH+) included patients with first-degree relatives that were diagnosed with dementia or parkinsonism. In this group, differences were made between maternal first-degree relatives (FHm) and paternal first-degree relatives (FHp). Patients with an unknown maternal or paternal first-degree relative, e.g. a brother or sister, were not included in these groups. Negative family history (FH-) included patients without first-degree relatives.

MRI imaging

MRI data was obtained using the standardized MRI protocol defined in the SOP for brain imaging in the PSI study (Aalten et al., 2014). A 1.5 or 3.0 Tesla scanner was used to acquire MRI images. To analyze the patient's brain volume, we used an automated quantitative method, in which gray matter volumes of 83 regions were calculated in ml (Bron et al., 2014).

To reduce multiple testing, six a priori defined regions of interest, known to be involved in AD, were chosen to analyze GMV: the medial temporal lobe, the hippocampus, the precuneus, the posterior cingulate cortex, the posterior temporal lobe, and the prefrontal cortex (Honea et al, 2010; Honea et al., 2011; Donix et al., 2010; Okonkwo et al., 2012, Wolters et al., 2017). These regions were specified according to the Hammers atlas, as can be seen in table 1 (Hammers et al., 2003).

Table 1. *ROI's specified by Hammers et al. (2003)*

ROI	***Specification by Hammers et al. (2003)***
Medial Temporal Lobe (MTL)	Hippocampus (left, right)
	Gyri parahippocampalis et ambiens (left, right)
Hippocampus	Hippocampus (left, right)
Precuneus	Superior parietal gyrus (left, right)
Posterior Cingulate Cortex (PCC)	Cingulate gyrus, posterior part (left, right)
Posterior Temporal Lobe (PTL)	Lateral occipitotemporal gyrus (left, right)
Prefrontal cortex (PFC)	Inferior frontal gyrus (left, right)
	Middle frontal gyrus (left, right)
	Superior frontal gyrus (left, right)
	Straight gyrus (left, right)
	Anterior orbital gyrus (left, right)
	Medial orbital gyrus (left, right)
	Lateral orbital gyrus (left, right)
	Posterior orbital gyrus (left, right)

Cognitive assessment

Cognitive assessment data were obtained through a standardized battery of cognitive tests (Aalten et al., 2014). We used the Mini Mental State Examination (MMSE) and the Clinical Dementia Rating scale (CDR) as screening instruments of

global cognition. To measure episodic memory, the delayed recall of the 15 Word-Auditory Verbal Learning Test (15-WVLT) was used (Brand & Jolles, 1985, as described in Aalten et al., 2014). We obtained measurement of verbal word fluency and semantic memory using the categorical Fluency, 60 seconds (animals) test (Lezak, 1995, as described in Aalten et al., 2014). Executive functioning was measured using the Trail Making Test (TMT), part A and B (Reitan, 1958, as described in Aalten et al., 2014). All tests were found sufficiently reliable and valid (Bowie & Harvey, 2006; Morris, 1997; Schmand, Groenink & van den Dungen, 2008; Tierney et al., 1994; Tombaugh, Kristjansson, McDowell & Hubley, 1996). To compare neuropsychological performances, raw scores of the 15-WVLT and the Fluency test of each patient were transformed into z-scores, using the mean and standard deviation of the test scores from the control group. Scores of the TMT were first reversed and then calculated into z-scores, so that higher scores indicate worse performance. Disease severity was calculated using CDR scores.

Statistical analyses

In the demographic data, differences between groups on continuous variables were analyzed using the analysis of variance (ANOVA) and post hoc independent sample t-tests. In case data did not meet the assumptions for parametric testing, the Kruskal-Wallis H test was used followed by Mann-Whitney U tests. Differences in the nominal variable gender were analyzed using Chi-square tests. CDR scores were compared across groups using the Mann-Whitney U test.

Before analyzing the GMV, correction for brain size was executed. This was done per individual, by dividing the sum of the ROIs volumes by the total intracranial volume (TIV). This resulted in volumes as a percentage of the TIV.

Subsequently, differences of GMV in the ROIs, and neuropsychological data (*dependent variables)* between FH+ patients, FH- patients and the control group (*independent variables),* were analyzed with a one-way analysis of covariance (ANCOVA). Data were split based on the occurrence of family history of dementia and parkinsonism. In case of GMV data, covariates were age, sex, disease duration, disease severity, as well as MRI vendor. In case of neuropsychological data, covariates were age, sex, disease duration, and disease severity. Disease duration was identified by looking at the difference in years between age of diagnosis and current age. If the assumption was violated a Kruskal-Wallis test was used, followed by Mann-Whitney

U tests when needed. Similarly, comparisons were made between FHm patients, FHp patients, FH- patients, and control patients. Prior to executing the ANCOVA, assumptions were tested by looking at homogeneity of variances, independence of residuals, and normality of residuals. To examine the homogeneity of variances, a Levene's test was used and parallelism of the lines expressing the linear relationships between the dependent variables and the covariates were checked. Normality of residuals was examined using histograms and skewness (S) and kurtosis (K) statistics. Of each group on each variable skewness and kurtosis z-scores were calculated and compared to a critical value, in which a z-score of more than |1.96| indicates a significant difference from the mean at $p < 0.05$ (Field, 2013). Furthermore, the significance of the Shapiro-Wilk statistics was checked. Control of outliers was executed by looking at the standardized residuals <|3|. No outliers were deleted since this did not lead to different results. To correct for multiple testing and reduce the chance of type-I error a Bonferroni correction was used. However, since this is an explorative study, uncorrected values are presented as well.

Lastly, to measure the relation between gray matter atrophy and cognitive performance in groups based on family history, a Pearson's R was used. Correlation analyses were performed between neuropsychological tests that were found statistically different between groups and the chosen ROI's. Differences between these within-group correlations were subsequently tested for significance using a Fisher's r to z transformation with Bonferroni correction. Before executing the analysis, linearity, outliers, and normality were checked. Linearity was tested by creating a scatterplot.

Analyses were run using the software Statistical Package for the Social Sciences, version 21 (SPSS Statistics, version 21.0, IBM Corporation). The α level was set at .05.

Results

Brain volume analysis in AD

Patient characteristics. Characteristics of AD patients and controls are shown in table 2. The percentage of men was significantly lower in all patient groups compared to controls, and the mean age was significantly higher in all patient groups relative to controls. Furthermore, MMSE scores were significantly lower in all patient groups as

compared with controls, and CDR scores were significantly higher in all patient groups as compared with controls.

Table 2. *Patient characteristics for AD patients of the brain volume analysis data.*

	Control (n=124)	FH+ (n=87)	FH- (n=93)	P value*	P value+	FHm (n=52)	FHp (n=23)	P value°
Gender, male (%)	87 (70.2)	39[a] (44.8)	46[a] (49.5)	**<.001**	.553	24[a] (46.2)	9[a] (39.1)	.572
Mean age in years (SD)	63.43 (10.281)	73.40[a] (8.785)	73,96[a] (10.497)	**<.001**	.702	72.90[a] (8.832)	73.48[a] (9.853)	.803
Disease duration in years (SD)	4.28[1] (4.185)	2.99[2] (2.079)	3.00[3] (2.983)	.186	.795	3.27 (2.134)	2.35 (1.584)	.077
Mean MMSE scores (SD)	28.36 (1.548)	23.95[a 4] (2.459)	24.35[a 5] (2.396)	**<.001**	.259	23.98[a 6] (2.345)	23.96[a] (2.440)	.920
Mean CDR scores (SD)	.62[7] (.598)	1.53[a 8] (.525)	1.42[a 9] (.579)	**<.001**	.114	1.49[a 10] (.505)	1.61[a] (.499)	.452

Note. Values are unadjusted means (standard deviation) or number of participants (percentages). MMSE: mini mental state examination. CDR: clinical dementia rating scale. Due to missing values, there is variance in n; [1:] n=86; [2:] n=91; [3:] n=51; [4:] n=118; [5:] n=86; [6:] n=91; [7:] n=51. *Differences between FH+ patients, FH- patients and controls by means of ANOVA, Kruskal-Wallis test, Mann-Whitney U or Chi-Square test. +Differences between FH+ and FH- patients by means of ANOVA, Kruskal-Wallis test, Mann-Whitney U or Chi-Square test. °Differences between FHm patients and FHp patients by means of independent sample t testing or Mann-Whitney U. a) post-hoc testing p <.05 compared with controls.

Gray matter volume. ANCOVA analyses with gender, age, disease duration, disease severity, and MRI vendor as covariates, showed smaller volumes in FH+ and FH- patients for the left and right MTL, hippocampus, precuneus, PCC, and PFC volumes in comparison with controls (table 3). For the left PTL volume, post-hoc analyses showed significantly smaller volumes in FH- patients compared with FH+ patients *(*$F(1,163)=6.504$, $\eta p^2=.038$), and significantly smaller volumes in FH- patients compared with controls ($F(2,288)=12.962$, $\eta p^2=.083$). For the right PTL volume, post-hoc analyses showed significantly smaller volumes in FH- patients compared with controls ($F(2,288)=5.683$, $\eta p^2=.038$).

Results of tests between controls, FHm and FHp patients showed significantly smaller volumes in FHm and FHp patients for the right and left MTL, hippocampus, precuneus, PCC, and PFC as compared with controls ($p < .001$). For the left PTL volume, post-hoc analyses showed significantly smaller volumes in FH- patients compared to FHm patients ($F(1,130)=6.111$; $p=.015$, $\eta p^2=.045$). After conducting the Bonferroni correction, this p-value did not remain significant. The unstandardized means and standard deviations of the ROI gray matter volumes in %TIV are listed in table 3.

Table 3. *Mean GMV in %TIV in specified ROIs with their accompanying p-values.*

	Control (n=118)	FH+ (n=86)	FH- (n=91)	P value*	P value+	FHm (n=51)	FHp (n=23)	P value°
MTL left, M (SD), ml %TIV	.00373 (.00042)	.00312[a] (.00045)	.00321[a] (.00052)	**<.001**	.260	.00318[a] (.00046)	.00296[a] (.00043)	.118
MTL right, M (SD), ml %TIV	.00378 (.00040)	.00319[a] (.00044)	.00323[a] (.00056)	**<.001**	.732	.00324[a] (.00048)	.00303[a] (.00039)	.148
Hippocampus left, M (SD), ml %TIV	.00130 (.00018)	.00106[a] (.00018)	.00110[a] (.00021)	**<.001**	.131	.00108[a] (.00017)	.00102[a] (.00019)	.274
Hippocampus right, M (SD), ml %TIV	.00142 (.00017)	.00119[a] (.00017)	.00122[a] (.00022)	**<.001**	.371	.00121[a] (.00018)	.00116[a] (.00018)	.522
Precuneus left, M (SD), ml %TIV	.01227 (.00141)	.01062[a] (.00141)	.01053[a] (.00160)	**<.001**	.860	.01069[a] (.00158)	.01031[a] (.00158)	.385
Precuneus right, M (SD), ml %TIV	.01221 (.00139)	.01064[a] (.00140)	.01042[a] (.00167)	**<.001**	.682	.01066[a] (.00133)	.01031[a] (.00162)	.551
PCC left, M (SD), ml %TIV	.00319 (.00042)	.00274[a] (.00050)	.00267[a] (.00055)	**<.001**	.726	.00271[a] (.00041)	.00268[a] (.00059)	.944
PCC right, M (SD), ml %TIV	.00317 (.00042)	.002743[a] (.00044)	.00263[a] (.00050)	**<.001**	.407	.00269[a] (.00037)	.00269[a] (.00052)	.865
PFC left, M (SD), ml %TIV	.04450 (.00446)	.03889[a] (.00491)	.03900[a] (.00533)	**<.001**	.472	.03939[a] (.00474)	.03722[a] (.00506)	.144
PFC right, M (SD), ml %TIV	.04609 (.00449)	.04069[a] (.00464)	.04090[a] (.00512)	**<.001**	.427	.04098[a] (.00434)	.03929[a] (.00521)	.186
PTL left, M (SD), ml %TIV	.00212 (.00036)	.00189 (.00034)	.00175[a] (.00034)	**<.001**	**.012**	.00192 [b] (.00036)	.00184 (.00029)	.739
PTL right, M (SD), ml %TIV	.00206 (.00036)	.00185 (.00037)	.00177[a] (.00032)	**.004**	.137	.00186 (.00033)	.00181 (.00034)	.374

Note. Values are unadjusted means (standard deviation) in %TIV. P-values are given comparing the groups with ANCOVAs. *Differences between FH+ patients, FH- patients, and controls. +Differences between FH+ and FH- patients. °Differences between FHm and FHp patients. Due to missing values of the covariate 'disease severity', a smaller n is used. [a:] post-hoc testing p <.05 compared with controls; [b:] post-testing p <.05 compared with FH-.

Cognitive performance analysis in AD

Patient characteristics. Characteristics of AD patients and controls included in the neuropsychological data analysis are shown in table 4. The percentage of men was significantly lower in all patient groups compared to controls, and the mean age was significantly higher in all patient groups relative to controls. Furthermore, MMSE scores were significantly lower in all patient groups as compared with controls, and CDR scores were significantly higher in all patient groups as compared with controls.

Table 4. *Patient characteristics for AD patients of the neuropsychological data pool.*

	Control (n=192)	**FH+ (n=123)**	**FH- (n=141)**	**P value***	**P value^{+}**	**FHm (n=67)**	**FHp (n=35)**	**P value°**
Gender, male (%)	127 (66.1)	60[a] (48.8)	69[a] (48.9)	**.001**	.539	31[a] (46.3)	17[a] (48.6)	.838
Mean age in years (SD)	64.10 (11.089)	73.37[a] (8.952)	73,83[a] (10.058)	**<.001**	.694	72.01[a] (9.279)	73.49[a] (8.651)	.341
Mean disease duration in years (SD)	4.18[1] (5.026)	3.09[2] (2.666)	3.12[3] (2.810)	.360	.795	3.22 (2.201)	3.14 (3.533)	.340
Mean MMSE scores (SD)	28.31[4] (1.561)	23.89[a 5] (2.461)	24.03[a 6] (2.516)	**<.001**	.622	23.84[a 7] (2.384)	24.07[a 8] (2.401)	.943
Mean CDR scores (SD)	.65[9] (.602)	1.53[a 10] (.517)	1.52[a 11] (.595)	**<.001**	.708	1.50[a 12] (.504)	1.54[a] (.505)	.683

Note. Values are unadjusted means (standard deviation) or number of participants (percentages). MMSE: mini mental state examination. CDR: clinical dementia rating scale. Due to missing values, there is variance in n; [1:] n=170; [2:] n=120; [3:] n=135; [4:] n=191; [5:] n= 121; [6:] n=138; [7:] n= 66; [8:] n=66; [9:] n=182; [10:] n=122; [11:] n=138; [12:] n=66. *Differences between FH+ patients, FH- patients, and controls by means of ANOVA, Kruskal-Wallis test, Mann-Whitney U or Chi-Square test. [+]Differences between FH+ patients and FH- patients by means of independent sample t testing, Kruskal-Wallis test, Mann-Whitney U or Chi-Square test. °Differences between FHm patients and FHp patients by means of independent sample t-testing or Mann-Whitney U. a) post-hoc testing p <.05 compared with controls.

Cognitive performance. Figure 1 displays the z-scores of the neuropsychological test performance of the groups based on the controls. All patient groups performed significantly lower on all neuropsychological tests compared with controls ($p < .001$), adjusted for gender, age, disease duration, and disease severity.

Analysis demonstrated a significant difference on the TMT A between FH+, FH- and the control group, $H(2) = 114.352$, $p < .001$. Post-hoc tests revealed that FH- patients performed significantly lower in comparison with FH+ patients $z = -2.122$, $p = .034$. Furthermore, a significant difference was shown on the TMT B between FH+, FH- and the control group, $H(2) = 193{,}597$, $p = <.001$. Post-hoc tests revealed that FH- patients performed significantly lower in comparison with FH+ patients, $z = -2.420$, $p = .016$. After conducting the Bonferroni correction, none of the p-values remained significant. No significant differences were found between FHm and FHp.

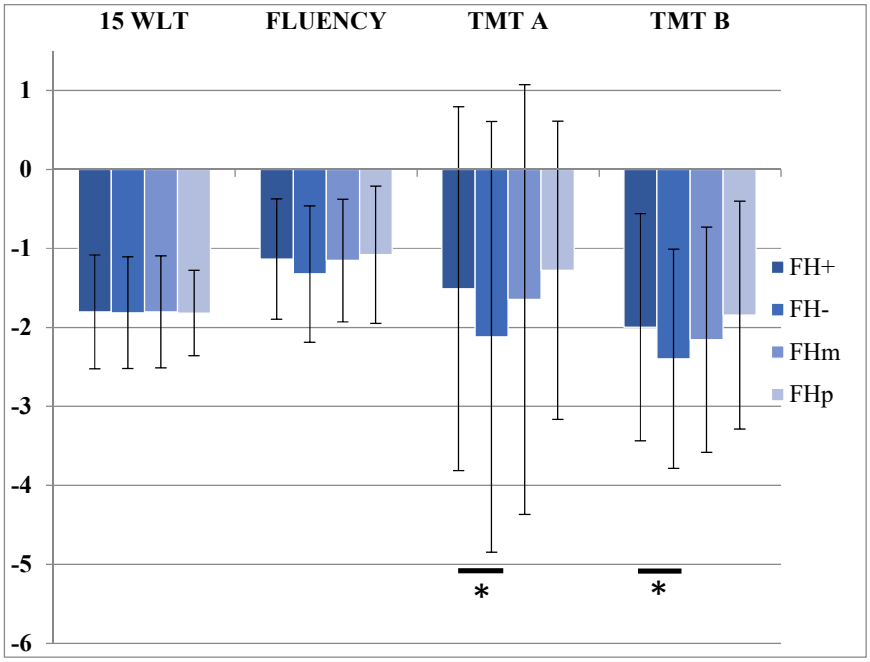

Figure 1. Z-scores of neuropsychological tests of the groups based on controls. Controls were by definition zero.
* indicate significant differences (p<.05) between FH+ patients and FH- patients.

Relation between cognitive performance and gray matter atrophy

Since significant differences were found in the TMT (A+B) between FH+ patients and FH- patients, a Pearson's R was used to test the relation between this test and GMV in the ROIs. After conducting the Fisher r-to-z transformation, no significant correlations were found in any of the patient groups.

Discussion

In the present study, we examined the influence of first-degree family history on gray matter atrophy and cognitive performance in patients with Alzheimer's disease.

We found that patients with a negative family history showed more gray matter atrophy in the left posterior temporal lobe compared with patients with a positive family history (uncorrected for multiple testing). Furthermore, patients with a maternal family history did not significantly differ from patients with a paternal family history. However, patients with a negative family history had more gray matter atrophy compared to patients with a maternal family history (uncorrected for multiple testing). Looking at the cognitive performance, we found that patients with a negative family history performed worse on the TMT A and B (a test that measures executive functioning) in comparison with patients with a positive family history (uncorrected for multiple testing). No correlation was found between gray matter volumes in the chosen regions of interest and performance on the Trail Making Test (A+B) in any of the patient groups.

The finding that patients with a negative family history showed more gray matter atrophy in the left posterior temporal lobe compared to patients with a positive family history, is contradictory to previous literature, which indicated more gray matter atrophy in AD-vulnerable regions in family history patients and in patients with a maternal family history (Ganske et al., 2016; Honea, Swerdlow, Vidoni, Goodwin, & Burns, 2010; Honea et al., 2011; Donix et al., 2010; Okonkwo et al., 2012). However, in most of these studies, the effects of family history were examined in cognitively healthy individuals with or without APOE-4 genotype (Honea, Swerdlow, Vidoni, Goodwin, & Burns, 2010; Honea et al., 2011; Donix et al., 2011; Okonkwo et al., 2012). In the current study, we included AD patients without controlling for APOE status. Although some studies found an effect of family history independently from APOE-4 (Donix et a., 2010; Johnson et al., 2006), a study performed by Lampert et al. (2014) shows no significant additional effect of family history on regional brain atrophy beyond the effect of APOE-4 in MCI patients. It therefore might be possible that the use of cognitively impaired patients, and the unadjusted effect of APOE-4 explain the dissimilar results found in this study. Yet, this finding is still quite interesting and suggests that patients with a negative family history are cognitively more impaired than patients with a positive family history. One might argue that individuals with a positive family history seek medical care earlier and perhaps get diagnosed earlier compared to patients with a negative family history, and thus are less affected. However, in this

study, family history groups did not significantly differ in disease duration and disease severity.

In our cohort, we found that patients with a negative family history had significantly smaller volumes in the left posterior temporal lobe compared to patients with a maternal family history. This result is inconsistent with previous literature, where more gray matter atrophy was reported in patients with a maternal family history compared to patients with a paternal or negative family history (Andrawis., 2012; Ganske et al., 2016; Honea, Swerdlow, Vidoni, Goodwin, & Burns, 2010; Honea et al., 2011). Studies performed by Honea et al. (2010; 2011), showed with voxel-based morphometry (VBM) on whole brain MRI data, gray matter reductions in AD-vulnerable regions, especially the precuneus and the prefrontal cortex, in cognitively healthy subjects. The different patient characteristics and method could explain our dissimilar result, since we chose to use MRI segmentation and ROI analysis to analyze GMV differences. Furthermore, according to Donix et al. (2012), patterns of risk variables manifested in family history risk, such as the APOE-4 allele, vary across different study populations and may even vary on the individual level. Since we did not include genetic status in our analysis, it might be possible that other risk variables associated with family history are overlooked. This could clarify the inconsistent finding.

In contrast with previous literature (LaRue et al., 2008; Wolf et al., 2005), findings in the current study indicate lower performance in executive functioning in patients with a negative family history compared to patients with a positive family history. However, these results are in line with the GMV results described earlier. In a study by Donix et al. (2012b), they investigated the influence of APOE-4 and family history on cognitive performance in healthy individuals and found that a positive family history of AD was associated with poorer performance in processing speed, executive functioning, memory encoding, and delayed memory at baseline. Other studies who examined the effect of family history on cognitive performance accounting for APOE-4, often used a single neuropsychological test or screening measures (LaRue et al., 2008; Hayden et al., 2009). In a longitudinal study of Hayden et al., (2009), they found no effect of family history and APOE-4 on cognitive decline. In the current study, several patients scored the lowest score possible, which makes it hard to detect further cognitive decline since there is a lack of variation. It might be possible that the effect

of family history on cognitive performance in cognitively impaired patients is difficult to detect because some patients are cognitively too severely affected (Donix et a., 2012a). This could also explain the non-significant correlation found between GMV reductions and cognitive performance. Furthermore, not accounting for APOE-4 genotype could have led to the dissimilar result found in this study. Yet, this result can be considered as unusual and more research in AD patients is needed to better understand the effect of family history on cognitive performance.

Results in this study indicate that patients with a negative family history are more affected than patients with a positive family history. Since this study is one of the first studies to investigate in cognitively impaired patients, this result could imply that having a positive family history does not have an influence on gray matter volumes and cognitive performance anymore when an individual is in a further stage of Alzheimer's disease. It might even be possible that disease course progresses faster in patients with a negative family history than patients with a positive family history.

However, since several studies show the combined effect of family history and APOE-4 on gray matter atrophy and cognitive performance (Hayden et al., 2009; Honea, Swerdlow, Vidoni, Goodwin, & Burns, 2010; Honea et al., 2011; Donix et al., 2011; Donix et al., 2012b; LaRue et al., 2008; Okonkwo et al., 2012), it is recommended to take the genetic status into account in future research. This might give a more complete view of how family history plays a role in gray matter atrophy and cognitive performance in AD patients.

A great strength in this research is the study design. Since we used data from a multicenter cohort study including patients nationwide, our results could be representative for all patients in the Netherlands who were seen in an academic hospital (Aalten et al., 2014). Furthermore, the use of standardized operating procedures (SOP) have led to an efficient and constant data collection in the different academic hospitals and resulted in meaningful data for clinical practice (Aalten et al., 2014). Lastly, the relatively large number of patients and controls in this cohort can be seen as one of the strengths of this study.

This study has some limitations. First, the system ProMISe (Project Manager Internet Server, Leiden, Netherlands) was used as a database for all collected clinical data from different academic medical centers. We experienced some difficulties with merging the data in this system in the same manner, which resulted in errors and missing

data when published. In future research, it might be valuable to not only use standardized operating procedures for collecting data, but also for entering data in this system to prevent such problems. Another limitation is that family history of dementia is provided by subject self-report data. It is known that reported prevalence rates of family history of dementia via self-report is lower than the exact prevalence due to poor recollection or censoring bias as a result of early parental death (Andrawis et al., 2012). However, there are several studies who examined family history by using self-report data (Andrawis et al., 2012; Donix et al., 2012a; Honea et al., 2011; Johnson et al., 2009), which makes our result still relevant. Furthermore, in our cohort, several patients scored the lowest score possible in tests measuring cognitive performance. Therefore, their cognitive performance was hard to interpret, and results should be interpreted with caution. Another limitation is that in this study a referral bias might occur, since we only included patients that were diagnosed in an academic hospital. Results can therefore not be generalized to populations who were referred to a general practitioner or local hospital (Aalten et al., 2014). Lastly, we chose to use a control group to identify profiles of the patient groups. However, using individuals with subjective cognitive complaints as our control group can be seen as a limitation. In literature, it is suggested that subjective cognitive complaints appear to be a risk factor for developing dementia and can already be present in the early stage of progression to AD (Mark & Sitskoorn, 2013; Reid & MacLullich, 2006). One might argue that using these individuals as a control group is not ideal, since they already experience cognitive complaints and might develop AD in the future.

In summary, findings in this study implicate that AD patients with a negative family history have more gray matter atrophy in the left posterior temporal lobe and perform worse on executive functioning than AD patients with a positive family history. This pattern suggests that patients with a negative family history are more affected, which is an unusual result that is not in line with previous literature. Therefore, this study is an interesting starting point for further research in this topic, since this could contribute to a better understanding of the effect of family history in AD patients.

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