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Individual cognitive and depressive traits associated with maternal versus paternal family history of Late-onset Alzheimer's disease: Proactive semantic interference versus standard neuropsychological assessments

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ABSTRACT

The main objective of this study was to assess cognitive and depressive manifestations associated with Alzheimer's disease in middle-aged asymptomatic individuals with maternal versus paternal family history of the disease using standardly used neuropsychological measures and a novel cognitive stress test, the Loewenstein-Acevedo Scale for Semantic Interference and Learning (LASSI-L). We evaluated cognitive abilities in offspring of late-onset Alzheimer's disease patients and a control group with no family history of dementia. Results showed lower cognitive performance in verbal episodic memory and semantic memory in participants with an Alzheimer's parent, especially in individuals with a maternal family history of the disease. While the standardly used neuropsychological evaluations were sensitive to differences in cognition between those with a maternal history of the disease and the control group, the LASSI-L was sensitive to proactive semantic interference impairments in both groups with a paternal and maternal family history of the disease. Depressive symptoms may affect cognitive performance differently in individuals with a family history of Alzheimer's disease compared to a control group, especially in individuals with a maternal history of the disease. This study highlights the value of semantic interference paradigms in early detection of Alzheimer's and emphasizes the importance of studying maternal versus paternal transmission of the disease.

1. Introduction

Alzheimer's disease is the most common form of dementia, accounting for 60–80% of dementia cases worldwide [1]. Late-onset Alzheimer's disease (LOAD) develops in patients aged over 65 years, comprises at least 95% of all Alzheimer's cases and is associated with confusion, memory problems, and behavioral changes [2,3]. Alzheimer's disease is characterized by two neuropathological hallmarks: extracellular plaques of amyloid beta (Aβ), which block cell-to-cell signaling, and intracellular Tau tangles, which impair the intracellular transport system, both of which cause cell death and lead to atrophy of several brain regions, including the cerebral cortex and the hippocampus [4].

Previous studies have evaluated cognitive phenotypes associated with late-onset Alzheimer's disease in asymptomatic individuals who are at-risk for developing the disease and identified specific patterns of cognitive decline beginning years before diagnosis of the disease, including impairments in episodic and semantic memory, executive functioning, and verbal intelligence [5–7]. A review of a longitudinal cohort and neuroimaging studies to determine correlations between

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brain biomarkers and specific cognitive functions in preclinical Alzheimer's disease showed that episodic memory was the most salient cognitive deficit, correlating with hypoconnectivity across large-scale brain networks and high levels of amyloid deposition in individuals with preclinical Alzheimer's disease [8].

After age, a family history of Alzheimer's disease is the second greatest risk factor for developing the disease [9,10]. Recent studies have suggested that the sex of the parent with Alzheimer's disease may also impact the development of Alzheimer's disease in their offspring, with some evidence in epidemiological studies indicating that maternal transmission may be more prevalent compared to paternal transmission of the disease [11]. Other studies have also shown that children of mothers with Alzheimer's disease have 3–9 times higher risk of developing Alzheimer's than those of fathers with the disease and that approximately 20% of all LOAD cases are maternally inherited – one study reporting a prevalence of 71.86% of maternal transmission compared to 28.14% of paternal transmission in a sample of subjects with family history of AD [12,13]. Some authors argue that maternally/inherited AD represents a different phenotype since these subjects present an earlier onset, lower scores on cognitive test and more pronounced AD-related brain abnormalities such as reduced brain metabolism, higher Aβ burden and decreased gray matter volume). Some of the suggested genetic mechanisms for maternal transmission are chromosome X-mediated transmission, genomic imprinting and through mitochondrial DNA transmission [14].

Depression may also play an important role in Alzheimeŕs disease because previous studies have shown that depressive symptoms are increased in preclinical Alzheimeŕs [15], depressed mood moderately increases the risk of developing Alzheimer's disease and other dementias [16], and the risk of dementia increases as the number of episodes of depression and bipolar affective disorder increases [17]. There is also evidence of a correlation between the Apolipoprotein e3/e4 genotype, a risk factor for Alzheimer's disease, and late-onset major depression [18]. Additionally, the prevalence of lifetime major depression is twice as high in women compared to men, making it a particularly important variable to study in relation to maternal versus paternal transmission of Alzheimeŕs disease [19]. Elevated anxiety symptoms in individuals with preclinical Alzheimeŕs disease have also been shown to play a role in the relationship between amyloid deposition and cognitive decline [20].

The objective of the present investigation was to determine if there are differences in cognition and depression in midldle-aged, asymptomatic individuals with a maternal history or paternal history of LOAD compared to a group of middle-aged individuals with no family history of dementia. In addition to a standardly used neuropsychological assessment battery, this study evaluated participants with a novel semantic interference paradigm using the Loewenstein-Acevedo Scale for Semantic Interference and Learning (LASSI-L), which has shown higher levels of sensitivity and specificity in discriminating between individuals with amnestic mild cognitive impairment (MCI) and healthy elderly individuals compared to standardly used neuropsychological measures of memory function [21]. Given the elevated sensitivity of this semantic interference test, we predicted that the LASSI-L would discriminate between individuals with no family history of dementia and individuals at-risk for Alzheimer's disease in both the maternal and paternal history groups, whereas standardly used neuropsychological measures would only be sensitive to discriminate cognitive deficits between at-risk individuals of Alzheimer's disease compared to the control group. In addition, we predicted that depressive symptoms would correlate with cognitive function differently in individuals with a family history of the disease compared to controls without a family history of dementia.

2. Methods

2.1. Design and sample

This was a cross-sectional study, where cognitive measures were compared between a sample of participants with a maternal family of Alzheimer's disease (FHm), a paternal family of Alzheimer's disease (FHp), and control subjects with no family history of dementia (CS). The study protocol was performed in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of FLENI Foundation, Argentina. All participants provided their written informed consent for the study. The sample size consisted of 22 individuals with a maternal history of Alzheimer's disease, 13 individuals with a paternal history of Alzheimer's disease, and 25 control subjects with no family history of dementia. The three groups were comparable in gender, age, and education level. The inclusion criteria for the offspring of participants with Alzheimer's disease were as follows: (1) one parent diagnosed with probable LOAD according to DSM-5, (2) 40–65 years of age at the time of recruitment, and (3) seven or more years of formal education. The control group had the same inclusion criteria except for a family history of AD. The exclusion criteria for all groups were as follows: (1) Mini Mental State Examination (MMSE) score < 25, (2) compromised intellectual level based on education and employment history, (3) evidence of current progressive neurological disease or likely to impair cognitive performance, (4) current and prior history of substance abuse (alcohol, marijuana, stimulants, benzodiazepines, or other drugs), and (5) Hachinski score > 7 (to exclude individuals with vascular-derived cognitive impairment).

2.2. Cognitive assessment

The methods describing the standardly used cognitive assessments in this study are described elsewhere [22]. The standardly used neuropsychological tests selected for this study have been widely validated and are frequently used in clinical practice. They consist of a concise battery aimed at assessing the most salient cognitive domains impaired in Alzheimer's disease: episodic memory and language. The neuropsychological evaluation was performed in a single session of approximately 90 min by an experienced neuropsychologist. The MMSE [23] and the Clock Drawing Test subtest from the 7 Minute Screen test [24] were included as screening measurements. Although the MMSE has been shown to be insensitive to prodromal Alzheimer's disease, we incorporated it as a widely used screening instrument [25] to be complemented with more sensitive tests. Verbal episodic memory was assessed by the Rey Auditory Verbal Learning Test [26,27]. Semantic memory was assessed by the semantic fluency task ("animals" category) [28], the Vocabulary subtest of the intelligence battery WAIS-III [29] and the Boston naming test [30]. Other verbal intelligence evaluations included an Argentine accentuation reading test of words (TAP-BA) to assess premorbid intelligence [31] and a phonologic fluency evaluation (letter "p") [32].

The Loewenstein-Acevedo Scale for Semantic Interference and Learning (LASSI-L) was designed to target the vulnerability to semantic interference in individuals with mild cognitive impairment at risk for developing Alzheimer's disease and is described in detail elsewhere [33]. The LASSI-L consists of two word lists (list A and list B), each with 15 words and 3 semantic categories: fruits, musical instruments, and articles of clothing. The investigator instructs the participant to read each word aloud as each word is presented individually. After reading all 15 words, the investigator then asks for the participant to recall as many of the words from the list as possible (free recall). The investigator then gives semantic cues for each category and asks for the

participant to recall as many words as possible in each semantic category (cued recall). The investigator then instructs the participant to repeat the exercise using the same list of words for a second learning trial. Participants are then presented again with semantic category cues and asked to recall words by category. The next part of the evaluation consists of the same tasks as the first part of the evaluation and uses the same 3 semantic categories, but with a different list of 15 words, eliciting proactive interference. An additional trial of List B assesses failure to recover from proactive interference (frPSI). Finally, without presenting the first list of words again, the investigator asks for a free recall followed by a cued recall of list A, evaluating retroactive interference. In the delayed recall section, participants are asked to recall words from both lists combined.

Some of the key features of the LASSI-L that differentiate it from standardly used neuropsychological evaluations include (1) explicit identification of the semantic categories used, (2) the use of a second list of semantically related target words, (3) using the same category cues for semantic interference and for the elicitation of semantic errors, and (4) evaluation of the failure to recover from proactive semantic interference (frPSI). For this investigation we focused on cued recall A2 (maximum storage and retrieval), B1 cued recall (susceptible to PSI), B2 cued recall (susceptible to frPSI) and short-delayed cued recall (subject to retroactive semantic interference (rSI). The LASSI-L cued learning score was calculated by averaging the scores of each semantic category on the cued recall portions of List A.

Because of the exploratory nature of the present study and one of its aims, which is the detection of subtle cognitive changes in comparable groups (age, sex and education level) of healthy middle-aged asymptomatic subjects, all cognitive tests measures were reported and analyzed as raw scores. Standardized scores in this case would obscure the detection of such small changes, which do not even constitute clinical deficits in performance given our sample's characteristics.

The Cognitive Reserve Questionnaire (CRQ) was administered to all participants to assess the most relevant elements associated to cognitive reserve (education level, parent's education level, additional academic courses completed, professional activity, musical education, fluent languages, reading activity, and ingenuity games) [34]. The concept of cognitive reserve refers to how individuals who engage in enriching cognitive activities may have a greater resistance to cognitive aging and dementia compared to those who do not have this enrichment [35]. The presence and severity of depressive symptoms was measured by the Beck Depression Inventory-II (self-report) and by the Hamilton Depression Rating Scale (HDRS), completed by a clinician. All participants were cognitively asymptomatic and their neuropsychological testing yielded normal values; none of the individuals met criteria for mild cognitive impairment or dementia.

2.3. Statistical analysis

Continuous variables were summarized by means and standard deviation. Categorical variables were summarized as frequencies and percentages. Differences in demographic and clinical data, standardly used cognitive assessments, and LASSI-L scores between groups were calculated by using Analysis of Variance (ANOVA). If significant main effects were found, pairwise difference was calculated using post hoc analysis by Tukey HSD tests. LASSI-L intrusion scores (> 1 intrusion, i.e. the proportion of participants with more than one intrusion) were calculated by means of the chi-square procedure. Correlations between clinical data and cognitive variables were evaluated using Pearson's correlation coefficients. We report two-tailed significance at $p < .05$. A false discovery rate was applied using the online SDM project false discovery rate (FDR) calculator for p values on Tables 1–3 [36]. Bolded p values indicate survival of the false discovery rate calculation. Kolmogorov-Smirnov test was performed to confirm normal distribution in all three sample groups. All statistical analysis was performed using SPSS version 22.0 software (SPSS Inc.).

3. Results

3.1. Demographic and clinical data

Table 1 shows the demographic and clinical characteristics of the subjects with maternal family history of Alzheimer's disease (FHm), paternal family history of Alzheimer's disease (FHp), and a control group with no family history of dementia (CS). The three groups were comparable in age and sex, as well as in education, chronotype, depression (as measured by the Hamilton Depression Rating Scale and Beck Depression Inventory-II), and Hachinski score (Table 1). Participants with a family history of Alzheimer's disease had lower cognitive reserve scores as compared to those without a family history of dementia, but this difference did not reach significance after adjustment of p values for the false discovery rate [FDR] (Table 1). The level of education of the parents of participants was not significantly different among the three groups (Table 1).

3.2. Standardly used neuropsychological evaluations

Table 2 shows significant differences between groups on standardly used cognitive assessments. Participants with a family history of Alzheimer's disease scored lower on several standardly used neuropsychological tests compared to the control group, including the Mini Mental State Exam (MMSE), several sections of the Rey Auditory Verbal Learning Test (RAVLT), and the vocabulary section of the Wechsler Intelligence Scale- III (WAIS-III) (Table 2).

Post hoc analysis showed participants with a maternal history of Alzheimer's disease scored significantly worse on several sections of the Rey Auditory Verbal Learning Test (RAVLT), including the delayed memory ($p = .003$), recognition ($p = .023$), and % retention ($p = .007$) scores, as well as the WAIS-III vocabulary test ($p = .003$), compared to the control group (Table 2). These differences on the RAVLT and the WAIS-III Vocabulary test were not observed among participants with a paternal history of the disease and the control group, or between participants with a maternal versus paternal history of Alzheimer's disease. Post hoc analysis also showed participants with a paternal history of Alzheimer's disease scored significantly lower than the control group on the Mini Mental State Exam ($p = .045$), though this difference was not observed between the control group and those with a maternal history of the disease. There were no significant differences in cognition between participants with a maternal versus paternal history of Alzheimer's disease (Table 2).

3.3. LASSI-L

Participants with a family history of Alzheimer's disease performed worse than controls on the LASSI-L (Table 3). Both groups with a family history of Alzheimer's had significantly more B2 cued intrusions than controls ($x^2 = 11.84$, $p = .003$). Individuals with a maternal history of the disease exhibited more intrusion errors on several sections of the LASSI-L compared to individuals with a paternal history of Alzheimer's disease and the control group, though these differences did not survive correction for multiple comparisons (Table 3).

3.4. Correlations between depressive symptoms and cognition

We sought to determine if there were correlations between the Hamilton Depression Rating Scale (HDRS) and performance on several cognitive evaluations. There was a significant negative relationship between the Hamilton Depression Rating Scale and the Mini Mental State Exam (MMSE) in the control group ($r = -0.493$, $p = 0.020$). In individuals with a maternal history of Alzheimer's disease, there was a negative relationship between the Hamilton Depression Rating Scale and the LASSI-L cued learning measure ($r = -0.685$, $p = 0.014$). There were no significant correlations between the Hamilton Depression

Table 1
Demographic and clinical data.

	Controls			Maternal History of AD			Paternal History of AD			f	p
	N	Mean or Frequency	SD or %	N	Mean or Frequency	SD or %	N	Mean or %	SD		
Age	25	51.17	8.223	22	54.45	9.354	13	52.69	6.473	0.892	0.416
Female	25	21	76%	22	18	72.7%	13	53.8%	6	2.608	0.082
Education (years)	25	18.17	3.200	22	16.76	2.705	13	18.00	3.536	1.076	0.349
Cognitive Reserve	24	17.88	2.787	22	15.18*	3.390	11	15.91	3.081	4.58	0.015
Cognitive Reserve- Parent Education	24	1.63	0.495	22	1.64	0.492	11	1.82	0.405	0.687	0.507
Chronotype (ICSP)	17	37.82	10.870	20	36.75	7.489	9	34.11	10.105	0.465	0.631
Hachinski Ischemic Score	20	0.85	1.040	21	1.24	1.221	11	5.27	14.227	1.846	0.169
Beck Depression Inventory-II	20	7.55	7.598	20	9.45	6.970	11	7.09	5.262	0.556	0.577
Hamilton Depression	22	7.18	5.439	22	9.09	7.584	11	7.09	5.873	0.594	0.556

(*) Indicates a significant difference of $p < .05$ between controls and one group of participants with a family history of Alzheimer's disease.

Rating Scale and LASSI-L scores in individuals with a paternal history of Alzheimer's disease.

4. Discussion

The purpose of this study was to evaluate an Alzheimer-associated cognitive phenotype in asymptomatic, middle-aged offspring of Alzheimer's patients and to investigate the development and progression of cognitive impairment in at-risk individuals based on the sex of the parent with the disease. Furthermore, we wanted to investigate if certain cognitive measures were more sensitive in differentiating between subtle cognitive deficits in asymptomatic, at-risk individuals compared to a control group with no family history of dementia and moreover if depressive symptom severity had a negative effect on cognitive performance in preclinical Alzheimer's disease.

The results support our hypothesis that that the sex of the parent with Alzheimer's disease may modify the cognitive abilities of asymptomatic, middle-aged offspring when compared to a control group without family history of the disease. These results highlight the deficits in verbal episodic and semantic memory in individuals with a maternal history of Alzheimer's disease and suggest that a standardly used battery of neuropsychological assessment is sufficient in detecting these subtle cognitive differences between offspring of mothers with Alzheimer's disease and a control group, but not between those with a paternal history of the disease and a control group with no family history of dementia.

Neuroimaging studies indicate that the progression of Alzheimer's may be different in individuals with a maternal family history of the disease, including hypometabolism of regions typically affected by Alzheimer's in FDG-PET scans of offspring of mothers with AD compared to offspring of fathers with Alzheimer's disease and a control group with no family history of the disease [37,38]. Additionally, individuals with a maternal history of Alzheimer's disease have greater atrophy in brain regions susceptible to AD compared to those with a paternal history of the disease and a control group [39]. One interpretation of these studies is that a maternal history of AD may lower the age of disease onset in the offspring [40]. Many of the traditional neuropsychological assessments were originally developed to evaluate dementia but are not necessarily optimal in evaluating the earliest stages of cognitive impairment in preclinical Alzheimer's disease [21]. However, a lower age of AD onset in individuals with a maternal history of Alzheimer's may explain why some of the traditional neuropsychological assessments detected subtle but significant cognitive differences between individuals with a maternal history of AD and controls but not between those with a paternal history of AD and the control group in the present study.

The obtained results support our hypothesis that the LASSI-L is more sensitive to subtle cognitive impairments in asymptomatic, at-risk individuals with a family history of Alzheimer's disease, regardless of maternal or paternal family history of the disease. As discussed elsewhere [21], the LASSI-L provides unique advantages for detecting cognitive deficits in semantic interference, which may reflect initial manifestation of the disease in at-risk individuals. The significant difference in cued intrusions for List B between both groups with a family history of Alzheimer's disease and a control group suggests that the LASSI-L is particularly sensitive to the subtle deficits in tasks involving proactive semantic interference, which may indicate the earliest manifestations of the disease.

A previous study evaluating the utility of the LASSI-L in early detection for Alzheimer's disease found that individuals with amnestic mild cognitive impairment (aMCI) had greater proactive and retroactive interference compared to normal elderly subjects [21]. Specifically, the second cued recall for both List A and List B were the strongest predictors of aMCI in logistic regression models and had a greater discriminatory power relative to delayed memory for passages, suggesting that evaluating semantic interference may be more powerful in detecting early features of Alzheimer's disease compared to other evaluations [21]. Other studies have found equivalent yet subtler semantic interference difficulties in asymptomatic middle-aged offspring of patients with Alzheimer's disease and such reduced performance was associated to structural changes in AD-relevant regions, increased amyloid load in the temporal lobe [41] and also exhibited inverse correlations with functional connectivity in limbic regions [42], providing evidence that deficits in semantic interference may represent

Table 2
Standardly used neuropsychological tests.

	Controls			Maternal History of AD			Paternal History of AD			f	p
	N	Mean	SD	N	Mean	SD	N	Mean	SD		
Mini Mental State Exam	24	29.63	0.711	22	29.00	0.976	12	28.75*	1.485	3.761	**0.029**
RAVLT Delayed Memory	23	11.00	2.111	21	8.19*	2.943	12	9.67	3.143	6.044	**0.004**
RAVLT Recognition	23	14.17	1.193	21	12.81*	2.182	12	13.33	1.303	3.791	**0.029**
RAVLT Retention	23	93.71	16.899	21	75.13*	22.068	12	83.563	18.288	4.981	**0.010**
WAIS-III Vocabulary	20	52.30	5.253	22	44.18*	8.198	12	46.67	9.509	6.163	**0.004**

(*) Indicates a significant difference of $p < .05$ between controls and one group of participants with a family history of Alzheimer's disease.

Table 3
LASSI-L measures.

	Controls			Maternal History of AD			Paternal History of AD			Statistic	P
	N	Mean or Frequency	SD or %	N	Mean or Frequency	SD or %	N	Mean or Frequency	SD or %		
A2 Cued Recall	21	14.19	1.030	12	13.83	1.030	10	13.60	1.265	f = 1.100	0.343
A2 Cued Intrusions	21	0.24	0.539	12	0.42	0.900	10	0.20	0.422	f = 0.398	0.674
> 1 A2 Cued Intrusions	21	1	0.0476	12	0.05	0.218	10	0	0	$X^2 = 0.855$	0.652
B1 Cued Recall	21	7.90	2.982	12	7.08	2.353	10	8.00	2.494	f = 0.653	0.430
B1 Cued Intrusions	21	0.95	1.322	12	2.50	3.030	10	1.90	1.853	f = 2.329	0.111
> 1 B1 Cued Intrusions	21	6	0.2857	12	6	0.5	10	4	0.4	$X^2 = 1.544$	0.462
B2 Cued Recall	21	12.24	1.700	12	11.42	1.505	10	11.30	1.494	f = 1.612	0.212
B2 Cued Intrusions	21	0.62	0.590	12	1.67	1.969	10	1.60	1.075	f = 3.713	0.033
> 1 B2 Cued Intrusions	21	1	0.0476	12	5*	0.4167	10	6*	0.6	$X^2 = 11.84$	**0.003**

(*) Indicates a significant difference of $p < .05$ between controls and at least one group of participants with a family history of Alzheimer's disease.

structural and limbic circuit dysfunction in early pathophysiology of Alzheimer's disease and that the LASSI-L should therefore be especially sensitive to subtle cognitive impairments in individuals with a family history of the disease. These studies support our findings that the LASSI-L can detect subtle cognitive differences between both maternal and paternal history of AD compared to a control group, as this tool was specifically designed to target the specific memory deficits in prodromal AD.

The negative correlations between the Hamilton Depression Rating Scale scores and cognitive assessments supported our hypothesis that depressive symptoms would have a different impact on cognition in individuals with a family history of Alzheimeŕs disease compared to the control group. Depressive symptoms correlated inversely with the MMSE in the control group, but not in individuals with a family history of Alzheimer's disease. Depressive symptoms correlated inversely with LASSI-L cued learning in individuals with a maternal history of Alzheimer's disease, but not in those with a paternal history of the disease or the control group, suggesting that depression may affect cognitive performance differently depending on the family history and sex of the parent with Alzheimer's. Previous studies also found that depression may affect cognition in preclinical and clinical Alzheimer's disease, as individuals with Alzheimer's disease but without depression tended to perform better on cognitive assessments than those with Alzheimer's disease and depression [43].

5. Conclusion

The results of this study confirm and extend previous observations that asymptomatic, middle-aged offspring of patients with Alzheimer's disease have subtle cognitive impairments compared to control subjects without a family history of the disease, including deficits in verbal episodic memory and semantic memory. These findings also support our hypothesis that standardly used neuropsychological tests highlight differences in cognition between individuals with a maternal inheritance of Alzheimer's disease and those without a family history of dementia, while the LASSI-L evaluation is more sensitive to cognitive impairments in both groups with a family history of Alzheimer's disease. The apparent increased cognitive deficits in at-risk individuals with a maternal history of the disease adds to the growing literature that the effects of Alzheimer's disease may differ depending on whether the disease is maternally or paternally inherited. Additionally, the sensitivity of the LASSI-L to proactive semantic interference in both groups with a family history of this disease provides further evidence that the LASSI-L can be a useful tool in research on early Alzheimer's disease manifestations. The correlations between depressive symptoms and cognition also suggest that depression may have a role in cognitive ability in individuals at-risk for developing Alzheimer's disease and may reflect an early phenotype of the disease, especially among those with maternal inheritance. However our sample size does not permit a definitive response to this issue which is open to further investigation.

One limitation of this study is the small sample size, especially in the number of participants with paternal inheritance. Whereas maternal inheritance revealed to exert a greater impact on cognitive performance than offspring with paternal inheritance – which is in line with the literature – it should be noted that any lack of influence on the paternal side could simply reflect inadequate statistical power due to the small number of cases for this sample group (n = 13). This becomes an important limitation in our study, since it was probably not powered enough to answer this essential question. In this regard, whereas results of offspring with maternal inheritance were compared to those with paternal transmission, we need to be careful when extrapolating these conclusions to the LOAD population because the lack of statistical power of the low sample size of the second O-LOAD might be hindering the detection of clinically meaningful differences. Apart from the issue with the O-LOAD with paternal inheritance sample size, an overall larger sample size is important for replication of these findings. A greater amount of subjects would allow for the analysis of LOAD related phenotypes in asymptomatic, at-risk individuals by both the sex of the parent with Alzheimer's disease and the sex of the participant, which may help us identify further sex differences in the disease and its transmission.

Future work for this study includes combining the current results with structural and functioning brain imaging data to further define neurodevelopmental characteristics associated with the Alzheimer's disease phenotype in offspring of patients with the disease and to determine if these results vary by the sex of the parent with the disease.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmip.2018.09.002.

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