



The executive prominent/memory prominent spectrum in Alzheimer's disease is highly heritable



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ABSTRACT

Late-onset Alzheimer's disease (LOAD) can present heterogeneously, with several subtypes recognized, including dysexecutive AD. One way to identify people with dysexecutive AD is to consider the difference between memory and executive functioning, which we refer to as the executive prominent/memory prominent spectrum. We aimed to determine if this spectrum was heritable. We used neuropsychological and genetic data from people with mild LOAD (Clinical Dementia Rating 0.5 or 1.0) from the National Alzheimer's Coordinating Center and the Alzheimer's Disease Neuroimaging Initiative. We cocalibrated the neuropsychological data to obtain executive functioning and memory scores and used their difference as a continuous phenotype to calculate its heritability overall and by chromosome. Narrow-sense heritability of the difference between memory and executive functioning scores was 0.68 (standard error 0.12). Single nucleotide polymorphisms on chromosomes 1, 2, 4, 11, 12, and 18 explained the largest fraction of phenotypic variance, with signals from each chromosome accounting for 5%–7%. The chromosomal pattern of heritability differed substantially from that of LOAD itself.

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1. Introduction

Alzheimer's disease (AD) is the most common form of age-related dementia, and most cases of AD occur late in life, referred to as late-onset AD (LOAD). Although LOAD subtypes are well recognized clinically and in research criteria for LOAD (Dubois et al., 2014), they are typically not considered in analyses aimed at elucidating the genetic architecture underlying LOAD (see, e.g., [Lambert et al., 2013; Naj et al., 2011]). People with dysexecutive AD,

a LOAD subtype, present with prominent executive dysfunction. Executive dysfunction refers to deficits in planning, judgment, reasoning, problem solving, organization, attention, abstraction, and mental flexibility (Stuss and Alexander, 2007).

One way to identify people with dysexecutive AD is to consider the difference between executive functioning and memory scores (Dickerson and Wolk, 2011; Mez et al., 2013a, 2013b; Mukherjee et al., 2012; Ossenkoppele et al., 2015). That difference defines an executive prominent/memory prominent spectrum, in which people with relatively intact executive functioning but profoundly poor memory performance are at 1 end, and people with relatively intact memory but profoundly poor executive functioning—that is, dysexecutive AD—are at the other. People with LOAD categorized in this way have been found to have distinct clinical, imaging, and genetic characteristics (Dickerson and Wolk, 2011; Mez et al., 2013a, 2013b; Mukherjee et al., 2012). Previous work suggests that the *APOE* ϵ 4 allele (chromosome 19) is less frequent in people with dysexecutive AD than that in people with more typical memory-prominent LOAD (Dickerson and Wolk, 2011; Mez et al., 2013a; Snowden et al., 2007). Beyond the *APOE* locus, however, it is unclear to what extent genetic versus nongenetic factors contribute to the executive prominent/memory prominent spectrum among people with LOAD.

We used neuropsychological and genetic data from 2 large US-based consortia to evaluate the heritability of the executive prominent/memory prominent spectrum among people with LOAD. We hypothesized that this spectrum would be heritable and furthermore that the pattern of heritability would be different from that of LOAD itself (Ridge et al., 2013).

2. Methods

2.1. Overview

We used a well-validated psychometric approach (Mukherjee et al., 2012) to cocalibrate neuropsychological data from the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI1) and National Alzheimer's Coordinating Center (NACC) databases. We constructed measures of executive functioning and memory from the neuropsychological testing data from these studies and used the difference between these scores as a continuous phenotype among people with LOAD. We used Genome-wide Complex Trait Analysis (GCTA; Yang et al., 2011) to calculate a lower bound for narrow-sense heritability, defined as the fraction of phenotypic variance explained by additive genetic effects. We estimated the heritability of this phenotype by chromosome and compared this chromosomal pattern of heritability with recently published chromosomal heritability estimates for LOAD (Ridge et al., 2013). We also performed a genome-wide association study of the difference between executive functioning and memory among people with LOAD.

2.2. Participants

ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether imaging measures, biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and mild AD.

NACC developed and maintains a large relational database of standardized clinical research data collected from the 29 National Institute on Aging—funded AD Centers and AD Research Centers. Each site enrolled participants and collected neuropsychological

data using a single neuropsychological battery, the Uniform Data Set. Data are uploaded to NACC regularly.

Data collection was approved by an institutional review board at each site. Informed consent was provided by each participant or, if they lacked capacity to consent, by legally authorized representatives.

Recruitment, participant evaluation, and diagnostic criteria for dementia, probable LOAD, and possible LOAD have been detailed elsewhere (Morris et al., 2006; Mueller et al., 2005; Weiner et al., 2010). Because we were interested in mild LOAD, we restricted our sample to people with a Clinical Dementia Rating (CDR) of 0.5 or 1.0 (Morris, 1993). Participants were either prevalent cases (i.e., were given a LOAD diagnosis at their initial study visit) or incident cases (i.e., were given a LOAD diagnosis at a follow-up study visit). For prevalent cases, we analyzed data from the baseline visit. For incident cases, we analyzed data from the first visit at which a LOAD diagnosis was made. Years of education were ascertained by self-report. We excluded participants aged less than 60 years.

ADNI and NACC have similar neuropsychological batteries, which include several tests of executive functioning and memory. Table 1 shows the executive functioning and memory tests administered. There were not sufficient indicators of language or visuospatial functioning to derive robust measures of these cognitive domains.

Table 1
Participant characteristics

Characteristic	ADNI (n = 302)	NACC (n = 624)	p-value ^a
Demographic characteristics			
Female (%)	129 (42.7%)	313 (50.2%)	0.03
Age in years, mean (SD)	76.1 (7.3)	79.0 (8.0)	<0.001
Education in years, mean (SD)	15.2 (3.0)	14.0 (3.1)	<0.001
<i>APOE</i> ϵ 4 carrier (%) ^b	203 (67.2%)	360 (59.4%)	
Global measures			
CDR 1.0 (%)	128 (42.7%)	438 (70.1%)	<0.001
MMSE, mean (SD)	23.6 (2.4)	21.6 (4.0)	<0.001
Executive functioning tests			
Animal list generation, mean (SD)	13.0 (5.0)	10.4 (4.7)	<0.001
Vegetable list generation, mean (SD)	8.2 (3.4)	6.7 (3.9)	<0.001
Trail making test part A, mean (SD)	60.6 (33.9)	69.6 (39.3)	<0.001
Trail making test part B, mean (SD)	187.1 (101.3)	217.0 (84.5)	<0.001
Digit span backward, mean (SD)	5.1 (2.0)	4.8 (1.9)	0.02
WAIS-R digit symbol, mean (SD)	29.1 (12.3)	24.9 (12.6)	<0.001
Clock drawing, mean (SD) ^c	3.5 (1.2)	X	
Memory tests			
Logical memory, immediate, mean (SD)	4.9 (3.2)	3.9 (3.4)	<0.001
Logical memory, delay, mean (SD)	1.5 (2.4)	1.6 (3.0)	0.61
RAVLT, trials 1–5, mean (SD)	23.1 (7.4)	X	
RAVLT, list B, mean (SD)	3.1 (1.3)	X	
RAVLT, immediate recall, mean (SD)	1.6 (1.8)	X	
RAVLT, delayed recall, mean (SD)	0.6 (1.5)	X	
RAVLT, recognition, mean (SD)	7.3 (3.9)	X	
ADAS-cog trials 1–3, mean (SD)	17.9 (4.2)	X	
ADAS-cog delayed recall, mean (SD)	8.5 (1.6)	X	
MMSE recall, mean (SD)	0.91 (0.99)	X ^d	

Key: ADAS-Cog, Alzheimer's Disease Assessment Schedule—Cognitive; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR, Clinical Dementia Rating Scale; MMSE, Mini-Mental State Examination; NACC, National Alzheimer's Coordinating Center; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

^a p-values were obtained using t-tests for continuous variables and Pearson χ^2 tests for categorical variables.

^b 18 people were missing *APOE* genotype data.

^c An X indicates that the test was not administered.

^d Although NACC administered the MMSE, scores for recall in particular were not available.

2.3. Genotyping, quality control, population substructure, and imputation

Methods for acquisition and processing of genotype data have been previously described (Naj et al., 2011; Potkin et al., 2009; Saykin et al., 2010). Briefly, for ADNI, the Human610-Quad BeadChip, and for NACC, the Human660-Quad or the OmniExpress BeadChips (Illumina, Inc. San Diego, CA, USA) were used for genotyping. The 2 *APOE* single nucleotide polymorphisms (SNPs; rs429358, rs7412) that define the ϵ 2, ϵ 3, and ϵ 4 alleles were genotyped separately (Naj et al., 2011; Potkin et al., 2009; Saykin et al., 2010).

Before imputation, for quality control (QC), we excluded SNPs with minor allele frequency <0.01, call rate <95%, or not in Hardy–Weinberg equilibrium ($p < 10^{-6}$). We excluded participants if reported sex differed from the sex designation established by X-chromosome analyses. We addressed cryptic relatedness within and across studies using KING software (Manichaikul et al., 2010) after performing linkage disequilibrium pruning on post-QC–genotyped SNPs. Our final “unrelated” data set ($n = 926$) excluded third degree or closer relatives (kinship coefficient ≥ 0.0442).

We evaluated population substructure in the 2 cohorts together. We only included individuals of self-reported European ancestry, as there were too few with non-European ancestry to derive meaningful results. We removed outliers whose genetic profiles were inconsistent with European ancestry. We used EIGENSTRAT (Price et al., 2006) to derive principal components based on common genotyped SNPs across studies.

We used IMPUTE2 (Howie et al., 2009) to perform genome-wide imputation of allele dosages separately for each cohort using the December 2010 1000 Genomes European ancestry reference panel (build 37) (Abecasis et al., 2012). We only included imputed SNP dosages with imputation quality ≥ 0.50 in both data sets. We combined the 2 data sets using PLINK (Purcell et al., 2007) and obtained a common set of 4,819,405 SNPs after a strict post-imputation QC that excluded SNPs with minor allele frequency <0.01 or call rate <98% on the combined data set.

2.4. Construction of the phenotype: the difference between executive functioning and memory scores among people with LOAD

Among ADNI participants, we previously developed composite memory (ADNI-Mem) and composite executive functioning (ADNI-EF) scores using modern psychometric approaches (Crane et al., 2012; Gibbons et al., 2012). ADNI-Mem and ADNI-EF encompass performance on all of the ADNI executive functioning and memory neuropsychological tests in Table 1. Lower scores for ADNI-Mem and ADNI-EF reflect poorer performance. Compared with individual test scores, each composite score was as good or better at detecting change over time, was more strongly associated with AD-related imaging parameters, and could better differentiate rates of decline between participants with mild cognitive impairment with and without AD cerebrospinal fluid signatures (Crane et al., 2012; Gibbons et al., 2012). As explained in the initial ADNI-EF article, we sought to maximize measurement precision for executive functioning by including as many indicators that reflected executive functioning as were available in the battery. This measurement precision comes at the expense of including indicators that may also reflect abilities in other domains such as visuospatial abilities or language (Gibbons et al., 2012).

Cocalibration refers to combining test scores across studies into a single metric. We cocalibrated ADNI-Mem and ADNI-EF scores with NACC item level data to obtain composite executive functioning and memory scores from NACC participants on the same metric as ADNI participants based on methods we previously

published (Crane et al., 2008). Overlapping test items between NACC and ADNI shown in Table 1 served as anchor test items administered in both studies. We used structural equation modeling with Mplus software (Muthen and Muthen, 1998–2004) to parameterize relationships between anchor test items. We then calculated executive functioning and memory scores for all NACC participants using ADNI-EF and ADNI-Mem parameters. We subtracted memory scores from executive functioning scores to create a difference score. A positive difference score reflects more memory than executive impairment, whereas a negative score reflects more executive than memory impairment.

For descriptive purposes we defined 5 groups: those with executive functioning >1 standard deviation (SD) worse than memory, those with executive functioning 0.5–1 SD worse than memory, those with executive functioning and memory within 0.5 SD of each other, those with memory 0.5–1 SD worse than executive functioning, and those with memory > 1 SD worse than executive functioning.

2.5. Narrow-sense heritability calculations

Narrow-sense heritability is defined as the proportion of phenotypic variance explained by additive genetic effects. We estimated heritability for our difference score with a mixed linear model that included all SNPs and treated their effects as random effects. We included directly genotyped SNPs and imputed SNPs as dosages. We included age, sex, genotyping platform and 3 principal components as fixed effects, and conducted analyses across all chromosomes and for each chromosome separately using GCTA software (Yang et al., 2011). We plotted chromosome-level findings alongside those previously published for LOAD (Ridge et al., 2013).

2.6. Other phenotypes

We used the same framework to estimate heritability of executive functioning alone and memory alone.

2.7. Genome-wide association study (GWAS)

We used linear regression in PLINK (Purcell et al., 2007) to perform a GWAS using the difference between executive functioning and memory, with the same analytic framework as for the heritability analyses.

2.8. Role of the funding sources

The funders of the study had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the article.

3. Results

Table 1 shows demographic and clinical characteristics and neuropsychological test performance among ADNI and NACC participants. NACC participants, on average, were 2.9 years older, had 1.2 fewer years of education, had a higher proportion of women, were somewhat more impaired on the CDR and Mini-Mental State Examination and were more impaired on all neuropsychological tests administered in both cohorts except logical memory delayed recall.

The distribution of the difference between executive functioning and memory among people with LOAD is shown in Table 2. The largest proportion of people with LOAD had memory scores >1 SD worse than executive functioning scores (44% in ADNI and 40% in NACC). Sizable proportions had executive functioning scores 0.5–1

Table 2
Distribution of differences between executive functioning and memory scores

Study	Executive functioning >1 SD lower than memory	Executive functioning 0.5–1 SD lower than memory	Executive functioning and memory within 0.5 SD	Memory 0.5–1 SD lower than executive functioning	Memory >1 SD lower than executive functioning	Total
ADNI	34 (11%)	21 (7%)	72 (24%)	41 (14%)	134 (44%)	302
NACC	84 (13%)	54 (9%)	137 (22%)	98 (16%)	251 (40%)	624

Key: ADNI, Alzheimer's Disease Neuroimaging Initiative; NACC, National Alzheimer's Coordinating Center; SD, Standard deviation.

SD below memory scores (7% in ADNI and 9% in NACC), and even more had executive functioning scores >1 SD below memory scores (11% in ADNI and 13% in NACC). In all, 18% of people with LOAD from ADNI and 22% of people with LOAD from NACC had executive functioning scores at least 0.5 SD worse than memory scores.

Some participants from NACC had autopsy data available, and some from ADNI had amyloid PET imaging and/or cerebrospinal fluid biomarker data available. We show data from those evaluations stratified by differences between executive functioning and memory scores in [Supplementary Tables 1–4](#). Although sample sizes for some of these investigations were small, with the data available to us, it appeared that people with executive functioning scores worse than memory had similar patterns of findings in these analyses compared with other people with LOAD (p -values: 0.1–0.7; see [Supplementary Tables 1–4](#)).

The narrow-sense heritability of the difference between executive functioning and memory was 0.68 (standard error = 0.12; p -value = 0.003) among people from NACC and ADNI with LOAD. SNPs on chromosomes 1, 2, 4, 11, 12, and 18 accounted for the largest proportion of the phenotypic variance, where combined signals from each of these chromosomes accounted for 5%–7% of the overall phenotypic variance ([Fig. 1](#)).

Phenotypic variance explained by each chromosome was not associated with chromosome length ($\beta = 0.38$; $p = 0.12$) or the number of genes on each chromosome ($\beta = 0.01$; $p = 0.98$).

In the same population, narrow-sense heritability for executive functioning itself was 0.10 (standard error = 0.22; p -value = 0.3), and narrow-sense heritability for memory was 0.01 (standard error = 0.21; p -value = 0.5). The chromosomal pattern of heritability for the difference between executive functioning and memory was distinct from that for executive functioning itself and memory itself (See [Supplementary Table 5](#) and [Fig. 1](#)).

Because *APOE* genotype had previously been implicated in the variation in executive functioning and memory in AD ([Dickerson](#)

and [Wolk, 2011](#); [Mez et al., 2013a](#); [Snowden et al., 2007](#)), we used linear regression under an additive model to test whether the *APOE* $\epsilon 4$ allele was associated with the memory score, the executive functioning score, or the difference between executive functioning and memory scores. After controlling for covariates, the *APOE* $\epsilon 4$ allele was associated with more impairment in memory ($\hat{\beta} = -0.10$; p -value = 0.03) and a larger difference score ($\hat{\beta} = 0.11$; p -value = 0.01) but was not significantly associated with executive functioning ($\hat{\beta} = 0.08$; p -value = 0.21).

In GWAS analyses, no SNPs achieved genome-wide significance.

4. Discussion

In this study, of 926 people with mild LOAD, 193 (21%) had executive functioning scores at least 0.5 SD worse than their memory scores, suggesting some degree of executive prominence. The executive prominent/memory prominent spectrum, defined by the difference between executive functioning and memory scores, was highly heritable with a narrow-sense heritability of 0.68 (standard error 0.12, p -value = 0.003). The executive prominent/memory prominent spectrum were much more heritable than executive functioning or memory separately. The chromosomal pattern of heritability of the executive prominent/memory prominent spectrum was distinct from the previously published pattern of heritability of LOAD ([Ridge et al., 2013](#)), with the largest signals on chromosomes 1, 2, 4, 11, 12, and 18.

Patients presenting with dysexecutive AD have distinctive pathologic, imaging, and clinical characteristics compared with patients presenting with more typical memory-prominent LOAD. A small case series found that patients with dysexecutive AD had disproportionate amyloid plaque and neurofibrillary tangle burden in the frontal lobes ([Johnson et al., 2005](#)). Patients with dysexecutive AD had greater frontoparietal cortical thinning than healthy controls or people with more typical memory-prominent AD ([Dickerson and Wolk, 2011](#)). Patients with dysexecutive AD declined more quickly on measures of cognition and daily functioning compared with patients with the more typical memory-prominent LOAD ([Mez et al., 2013b](#)). A recent article using a similar approach adds additional support to the notion that dysexecutive AD has distinct imaging and clinical characteristics compared to more typical memory-prominent LOAD ([Ossenkoppele et al., 2015](#)).

This study provides evidence that the executive prominent/memory prominent spectrum among patients with LOAD is highly heritable. Our calculation of 0.68 may reflect a lower bound for narrow-sense heritability because it does not consider additional genetic effects from rare variants and from gene \times gene or gene \times environment interactions. Recently [McLaughlin et al.](#) discussed GCTA versus twin study–based heritability estimates and noted that GCTA may provide a lower bound on heritability ([McLaughlin et al., 2015](#)). Furthermore, they suggest that differences between GCTA-based heritability estimates and twin study–based estimates may be useful to understand missing heritability. The present report is the first to address heritability of the executive prominent/memory prominent spectrum among people with LOAD; there are no twin studies we are aware of. Future studies may address this,

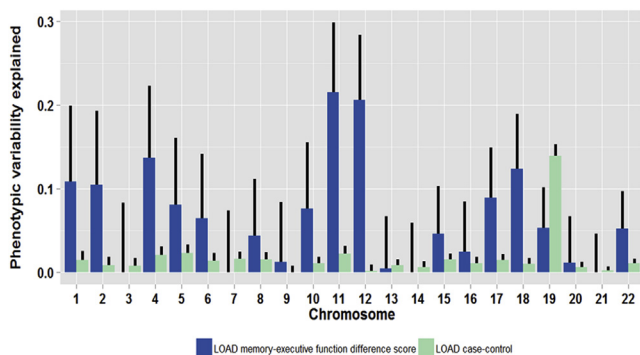


Fig. 1. Chromosomal phenotypic variability. Phenotypic variability explained by each chromosome for the continuous LOAD executive functioning–memory difference score (blue) and dichotomous LOAD case-control status (green). The LOAD executive functioning–memory difference score was derived using cocalibrated executive functioning and memory composite scores from the Alzheimer's Disease Neuroimaging Initiative and the National Alzheimer's Coordinating Center. The LOAD case-control phenotypic variability was derived previously using data from the Alzheimer's Disease Genetic Consortium ([Ridge et al., 2013](#)).

though such studies would need a large number of pairs of twins with LOAD and available neuropsychological data.

The study also demonstrates that genetic factors associated with LOAD risk appear to be different from genetic factors associated with the executive prominent/memory prominent spectrum among people with LOAD. For instance, chromosome 11 variants explain the greatest amount of phenotypic variability for the executive prominent/memory prominent spectrum but only explain a small amount of LOAD's phenotypic variability. Conversely, chromosome 19 variants, which include *APOE* genotypes, explain a substantial proportion of LOAD's variability but only a small proportion of the variability of the executive prominent/memory prominent spectrum (Fig. 1).

This work confirms and extends previous findings relating to *APOE* genotype (Dickerson and Wolk, 2011; Mez et al., 2013a; Snowden et al., 2007), i.e., that people with LOAD with ≥ 1 *APOE* $\epsilon 4$ allele are more likely to have the more typical memory-prominent AD than to have dysexecutive AD. This work places those findings in a broader context. Although we replicated the finding, the *APOE* $\epsilon 4$ effect did not approach genome-wide significance, and variants on other chromosomes contributed substantially more to the variability of the executive prominent/memory prominent spectrum among people with LOAD. This finding should be understood in the context of the sample we studied, which has a higher proportion of people with *APOE* $\epsilon 4$ than the general population. Other than our own prior analysis of the ADNI data set (Mukherjee et al., 2012), genetic analyses of dysexecutive AD have been limited to the *APOE* genotype (Dickerson and Wolk, 2011; Mez et al., 2013a; Snowden et al., 2007). Our results suggest the need for additional work in this area. Future studies may also consider incorporating data from cognitively normal elderly controls.

To date over 20 genetic loci have been identified to be associated with the risk of LOAD (Lambert et al., 2013). The field has been characterized by coordinated efforts to search for variants associated with LOAD risk using ever-larger coalitions of research studies and more genetic variants. Less attention has been paid to genome-wide genetic analyses of LOAD subtypes.

Our study has several weaknesses, mainly stemming from the modest sample size. Larger samples would reduce the standard error, providing a more precise estimate of narrow-sense heritability. Narrow-sense heritability estimates for chromosomes 3, 7, 14, and 21 failed to converge, likely because of sample size. Predictably, given our sample size, no single variant achieved genome wide significance in our genome wide association analyses. We were not able to compare findings from the NACC data to those from the ADNI data. Nevertheless, our analytic strategy is scalable. We plan to augment our sample by evaluating neuropsychological and genetic data from additional cohorts. Although ADNI focuses on early-stage LOAD and NACC includes people from across the LOAD-severity spectrum, we enhanced comparability by restricting study participants to those having a CDR of 0.5 or 1.0. Only a subset of participants in these studies had neuropathology or fluid biomarker data. Once larger samples are available, it will be important to repeat these analyses among people with biomarker confirmation of AD pathology. Because of the cognitive data collected by these studies, we are not able to firmly conclude that our findings are related specifically to executive functioning and not other domains such as language or visuospatial ability. Nevertheless, our findings strongly support the notion that there is considerable cognitive domain heterogeneity among people with LOAD and that this heterogeneity has a strong genetic component that is distinct from the genetic architecture of LOAD itself. ADNI and NACC are large convenience-based samples. It will be important to compare findings across other study designs to determine the extent to which idiosyncrasies in enrollment criteria and research focus may have an influence on findings.

Although evaluation of the genetic architecture of disease subtypes has been applied in several conditions, especially congenital heart disease (Cordell et al., 2013), its use in neurogenetics is rare (Girard and Rouleau, 2014). A recent article on frontotemporal dementia (FTD) used a similar strategy to evaluate genetic architecture of FTD subtypes (Ferrari et al., 2014). That study identified the *C9orf72* locus with genome-wide significant findings in people with overlapping motor neuron disease but not in other FTD subtypes and not in the combined group of everyone with FTD. These findings, together with those presented here, suggest that the disease subtype approach may be a valuable strategy to further our understanding of the genetic architecture of other neurodegenerative conditions (Ferrari et al., 2014), including LOAD.

5. Conclusions

About one-fifth of the people from 2 prominent studies of LOAD have executive functioning scores substantially lower than the memory scores. Genetic variation explains at least 2/3s of the variance of this executive prominent/memory prominent spectrum among people with LOAD. The pattern of phenotypic variability explained by SNPs on each chromosome differed substantially from that of previously published findings for LOAD. Our results suggest that different genes—and thus different biology—may be responsible for executive prominence among people with LOAD. Future studies should specifically address heterogeneity among people with LOAD.

Disclosure statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neurobiolaging.2016.02.015>.

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