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Incidence of cognitively-defined late-onset Alzheimer's dementia subgroups from a prospective cohort study

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Abstract

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Supplementary data

Supplementary data related to this article can be found at (url).

INTRODUCTION—There may be biologically relevant heterogeneity within typical late-onset Alzheimer's dementia.

METHODS—We analyzed cognitive data from people with incident late-onset Alzheimer's dementia from a prospective cohort study. We determined individual averages across memory, visuospatial functioning, language, and executive functioning. We identified domains with substantial impairments relative to that average. We compared demographic, neuropathology, and genetic findings across groups defined by relative impairments.

RESULTS—During 32,286 person-years of follow-up, 869 people developed Alzheimer's dementia. There were 393 (48%) with no domain with substantial relative impairments. Some participants had isolated relative impairments in memory (148, 18%), visuospatial functioning (117, 14%), language (71, 9%), and executive functioning (66, 8%). The group with isolated relative memory impairments had higher proportions with *APOE ε4*, more extensive Alzheimer's-related neuropathology, and higher proportions with other Alzheimer's dementia genetic risk variants.

DISCUSSION—A cognitive subgrouping strategy may identify biologically distinct subsets of people with Alzheimer's dementia.

Keywords

Alzheimer's disease; cognition; subgroups; endophenotypes; heterogeneity; genetics; neuropathology

1. Introduction

There may be considerable heterogeneity in clinical presentation among people with incident Alzheimer's dementia begging the question of whether Alzheimer's dementia in older adults should be considered a single entity or meaningfully subdivided into distinct disorders. Meaningfully subdividing a condition into distinct groups is essential to the strategy of personalized medicine[1–3]. Data are currently lacking demonstrating a scalable approach for meaningfully subdividing Alzheimer's dementia.

Recent proposed guidelines identified atypical Alzheimer's disease subtypes usually having younger age of onset, including logopenic primary progressive aphasia, dysexecutive Alzheimer's disease, and posterior cortical atrophy[4]. Intriguingly, each of these subtypes is associated with prominent impairment in a single non-memory domain – language, executive functioning and visuospatial functioning, respectively – with relatively intact memory performance. These previously identified atypical Alzheimer's disease subtypes may represent extremes of a spectrum of disease phenotypy.

We followed insights from neuropsychology, where practitioners have considered patterns of relative impairments across cognitive domains to facilitate diagnosis since the earliest days of the field[5]. We used cognitive data to determine the distribution at Alzheimer's dementia diagnosis for memory, language, executive functioning, and visuospatial abilities in a community-based prospective cohort study. We determined individual averages across domains, and identified domains with substantial impairments relative to that average. We

defined subgroup membership based on which domains had relative impairments. We compared demographic, neuropathology, and genetic findings across subgroups to test the hypothesis that we could use cognitive data to identify biologically distinct late-onset Alzheimer's dementia subgroups.

2. Methods

We followed the STROBE guidelines (Appendix A)[6]. All steps are summarized in Appendix B.

2.1. Study population

The source population for the Adult Changes in Thought (ACT) study consists of community-living members of Group Health, a health maintenance organization in western Washington State. A random sample of community-living Group Health members ≥65 years old without established dementia diagnoses was invited to an enrollment visit in 1994–1996. The Cognitive Abilities Screening Instrument (CASI) was administered. The CASI is a 100-point scale that assesses several cognitive domains. Individuals with scores >85 were invited to enroll. Those with scores of ≤85 were further evaluated with a neuropsychological battery and comprehensive neurological evaluation. The neuropsychological battery included clock drawing[7], verbal fluency[8], Mattis Dementia Rating Scale[9], Boston naming[8], verbal paired associations and recall, logical memory and recall[10], Word List Memory[8], Constructional Praxis and recall[8], Trails A and B[11], and Information and Comprehension subtest items[10].

All cognitive and clinical data were reviewed in a multidisciplinary consensus conference to determine dementia status; data from each case are discussed and forms with standardized criteria are filled out. Composite scores were not available at the time of consensus conferences and were not considered. Individuals free of dementia were invited to enroll in the longitudinal study. Identical methods were used for an expansion cohort in 2000–2003. In 2005 the study began continuous enrollment in which identical methods are used to enroll new participants each month. This report considers all enrollees through April 2015, the most recent data freeze.

Once enrolled, participants are administered the CASI every two years. The same procedures are used to identify incident dementia[12] and probable or possible Alzheimer's disease using NINCDS-ADRDA criteria[13], referred to here as Alzheimer's dementia.

Other than being a Group Health member, being free of dementia, and volunteering for a longitudinal study, there are no additional inclusion or exclusion criteria for ACT. ACT evaluates participants in their own homes or at a study clinic for study visits[14].

We focus here on individuals who developed incident Alzheimer's dementia. The derivation of the analytic cohort is provided in Figure 1. The study was reviewed by Group Health and University of Washington Institutional Review Boards. Participants gave written informed consent.

2.2. Ascertainment of subgroups

An expert panel (ET, AS, and JM) considered each cognitive item and assigned each item to a single cognitive domain – memory, visuospatial functioning, language, executive functioning, or other. We used modern psychometric methods to obtain scores for each domain. Composite scores have been recommended to address idiosyncrasies of individual cognitive tests. Modern psychometric approaches have proven to have incrementally better validity data than scores derived from standard approaches[15–17], and they are specifically recommended for genetic analyses[18]. We re-coded observed item responses to avoid sparse response categories and limit to ≤10 response categories (see Appendix C–F). We used Mplus 7.4[19] to fit confirmatory factor analysis single factor or bifactor models for each domain separately. All scores were scaled to have mean 0 and standard deviation (SD) 1 in all those with incident AD who had all four scores (n=825). Psychometric modeling details for each domain are provided in Appendix C–F.

We determined each person's average across the four cognitive domain scores. We determined relative impairments by calculating differences between each domain score and the individual's average cognition score across domains. We evaluated candidate thresholds to define "substantial" relative impairments ranging from 0.40 to 1.25 points at 0.05-point increments. For each candidate threshold, we classified people as having 0, 1, or ≥2 domains with substantial relative impairments; we further divided those with 1 domain according to which domain was relatively impaired. This approach is illustrated in Box 1, where we analyze domain scores for a made-up person and for two real people from ACT diagnosed with atypical Alzheimer's disease using the same methods described above. We further illustrate performance on a single selected test from each domain in Box 2.

As discussed in Appendix G, we empirically selected a threshold of 0.75 points. We compared characteristics of groups defined by that threshold.

2.3. Neuropathology procedures

ACT Neuropathology protocols are published[20,21]. We evaluated neurofibrillary tangles as measured by Braak stage[22], neuritic plaque frequency according to CERAD[23], presence of cerebral amyloid angiopathy, presence of hippocampal sclerosis, presence and location of Lewy bodies categorized as present anywhere and as present in the amygdala, presence of cystic infarcts, and presence and location of cerebral microinfarcts categorized as present anywhere, in the cortex, or in deep structures (basal ganglia or thalamus). We present findings for the group of ACT participants who died free of dementia, for everyone who died following diagnosis of Alzheimer's dementia, and separately for those in each cognitively defined subgroup. ACT does not identify people with mild cognitive impairment (MCI); people who died free of dementia could include some people with MCI. The neuropathology results presented here exclude people who died with non-Alzheimer's dementia.

2.4. Genetic data

APOE genotyping was available for most participants[24]. ACT participants with European ancestry were included in the Alzheimer's Disease Genetics Consortium (ADGC)[24] and the International Genomics of Alzheimer's Project (IGAP)[25] meta-analyses of genome-wide

single nucleotide variant (SNV) associations with late-onset Alzheimer's dementia. Genotyping, quality control, and imputation procedures are detailed in those publications. We used imputed genotype dosage data for the SNV with the highest level of association at each of the 20 loci that achieved genome-wide significance in the Lambert et al. IGAP paper[25] ("IGAP SNVs").

2.4. Statistical analyses

Group differences in descriptive findings were compared using linear or logistic regression, as appropriate, and a categorical group variable with "no domain" identified as the reference. We used similar models for autopsy findings, controlling for age at death, sex, and years of education.

For genetic analyses, we used non-demented elderly individuals from ACT as the reference group (some of these individuals could have had MCI), and included terms for age, sex, and three principal components to account for population stratification. As in[26], we did not adjust for *APOE* genotype. We determined odds ratios for each IGAP SNV for all people with Alzheimer's dementia, and separately for each cognitively-defined subgroup.

3. Results

3.1. Characteristics of individuals with incident Alzheimer's dementia

As of April 2015 ACT had enrolled 5,088 people, of whom 4,365 had at least one follow-up. Over 32,286 person-years of follow-up (mean 8.1) 1,076 people developed dementia[12], of which 869 developed probable or possible Alzheimer's disease by NINCDS-ADRDA criteria[13], referred to here as Alzheimer's dementia. We had sufficient data to compute all four cognitive domain scores for 825 (95%) of these; most of the remainder had only a phone-based CASI without visuospatial functioning assessment.

On average people with Alzheimer's dementia performed much worse than people with normal cognition, especially for memory; see Box 2 for examples of test scores (one per domain) alongside published normative data[27,28]. We used means and standard deviations from the 825 people from ACT with incident Alzheimer's dementia and all four domain scores to define the metric (mean=0, SD=1) for each domain.

We identified a threshold of 0.75 points as a threshold indicating substantial relative impairment (See Appendix G). At that threshold, there were 393 people (48%) who had no domains with a substantial relative impairment. There were 396 people (48%) with a substantial relative impairment in a single domain, including 148 with a substantial relative impairment in memory (18%), 117 in visuospatial functioning (14%), 71 in language (9%), and 66 in executive functioning (8%). The remaining 30 people (4%) had substantial relative impairments in ≥2 domains.

Demographic characteristics of people with incident Alzheimer's dementia in each cognitively-defined subgroup are shown in Table 1, along with *APOE* genotype and cognitive data. There were no important differences across groups in demographic characteristics, including age at dementia onset. There were substantial differences in the

proportion of people with incident Alzheimer's dementia who had at least one *APOE* ε4 allele, ranging from 45% of those with isolated relative memory impairment to 22% of those with isolated relative executive functioning impairment; the overall χ^2 p-value for *APOE* was 0.005.

Averages for cognitive scores are also shown in Table 1. For most groups, average CASI total scores were similar to the overall average for people with incident Alzheimer's dementia, though they were somewhat higher for people with relative visuospatial functioning impairments (p=0.01) and perhaps somewhat lower for those with relative executive functioning impairments (p=0.61) and especially those with multiple domains with relative impairments (p=0.02). The CASI total score includes 10 points for visuospatial functioning and 12 points for executive functioning, so 10% of the total score is based on executive functioning and 12% on executive functioning, while our average scores included other measures of these domains and also assigned each of them to 25% of the total average score.

By design, average scores across the entire group of people with incident Alzheimer's dementia for each cognitive domain were 0 with SD=1. People with no domains with a substantial relative impairment had average overall scores and average domain scores that reflected these patterns. The four groups made up of people with a single domain with relative impairments had mean scores for the indicator domain about a full standard deviation below average (about −1.0), while scores for the other domains were close to the average (about 0.0) or a little better than the average. On average, the group with multiple domains with relative impairments had lower scores on non-memory domains.

3.2. Autopsy findings

Autopsy findings are summarized in Table 2. Of the 825 people with incident Alzheimer's dementia and all four cognitive domain scores, 180 had died and come to autopsy at the time of this report. We evaluated data from those individuals and people who died without a diagnosis of dementia; people with non-Alzheimer's dementia are not included in Table 2.

Most neuropathological findings were more common among people with Alzheimer's dementia than people with no dementia (all p <0.023, with the exception of Lewy bodies). The frequency and mean severity of most neuropathological findings were similar across cognitively-defined subgroups. Having a Braak stage of IV or higher was more common among people with substantial relative memory impairment (91%) than among everyone else with Alzheimer's dementia (68%, p=0.003), and the proportion of people with amyloid angiopathy was also higher, though this did not meet the traditional statistical significance threshold (50% vs. 35%, p = 0.08).

3.3. Genetic findings

Genetic findings are summarized in Table 3. The fifth column of Table 3 shows odds ratios (ORs) for the association between the 20 SNVs reported in Lambert et al.[25] and Alzheimer's dementia case-control status in ACT. In general, findings in ACT were similar to those previously reported[25]. The remaining 6 columns of Table 3 show ORs for the associations between the 20 IGAP SNVs and case-control status, where "cases" were limited to

individuals in a cognitively-defined subgroup. While we were underpowered for genetic association analyses with data from a single study, we nevertheless marked “extreme risk ORs” (defined as OR>1.30) in shades of red, and “extreme protective ORs” (defined as OR<1/1.30~0.77) in shades of blue.

ORs for those with no domain with substantial relative impairments were broadly similar to those for the entire group of people with Alzheimer’s dementia, though there were somewhat smaller ORs for the SNV associated with *CR1* and *MS4A6A*, and somewhat larger ORs for the SNVs associated with *ABCA7* and *CD33*. For the subgroups of individuals with a single domain with a substantial relative impairment, findings were quite heterogeneous. There were eight extreme risk ORs for the group with an isolated relative memory impairment. There were nine extreme risk ORs (6 risk, 3 protective) for the group with an isolated relative visuospatial functioning impairment, and nine extreme risk ORs for the group with an isolated substantial language impairment (4 risk, 5 protective). There were six extreme risk ORs for the group with an isolated relative executive functioning impairment (4 risk, 2 protective). The small group with multiple domains with relative impairments had fifteen extreme risk ORs (nine risk, 5 protective).

There were several SNVs with extreme protective ORs for at least one cognitively defined subgroup (blue cells) and extreme risk ORs for at least one other subgroup (red cells), including SNVs associated with *SORL1*, *FERMT2*, *CASS4*, *PTK2B*, *ZCWPW1*, and *NME8*.

4. Discussion

4.1. Key findings

We developed and implemented an approach to identify subgroups of people with typical late-onset Alzheimer’s dementia on the basis of cognitive test data. We generated scores for four domains – memory, visuospatial functioning, language, and executive functioning – and characterized variation in these scores in a large group of people with incident Alzheimer’s dementia. We determined each individual’s average level of cognition at Alzheimer’s dementia diagnosis. We then determined differences from this average to identify domain(s) with substantial relative impairments. About half of people with incident Alzheimer’s dementia had no domains with a substantial relative impairment, and a similar number of people had a single domain with a substantial relative impairment.

Demographic characteristics were similar across each of the cognitively defined subgroups, including age at the time of Alzheimer’s dementia diagnosis. This point emphasizes a distinction with the atypical Alzheimer’s disease subtypes such as posterior cortical atrophy and primary progressive aphasia identified by the International Working Group[4]; each of these is described as having an earlier age of onset than is typical for late-onset Alzheimer’s dementia, and certainly earlier age of onset than the mid to late 80s as we found for each subgroup and overall (see Table 1). These atypical Alzheimer’s disease subtypes may occasionally be found in older adults, as demonstrated by the fact that there was one person each with posterior cortical atrophy and with primary progressive aphasia in ACT (see Box 1). Our approach to categorizing people with typical late-onset Alzheimer’s dementia, when

applied to those individuals with previously defined atypical Alzheimer's disease subtypes, worked precisely as one would wish – the person with posterior cortical atrophy had an intact memory score and a substantial relative impairment in visuospatial functioning, while the person with primary progressive aphasia had an intact memory score and a substantial relative impairment in language (see Box 1). Additional analyses will be necessary to determine relationships between people diagnosed with PPA, PCA, and dysexecutive Alzheimer's disease and people we identify with isolated substantial relative impairments in language, visuospatial functioning, and executive functioning.

The group with isolated substantial memory impairment stood out from the other groups. Using only cognitive testing data for our group assignments, we identified this group of 18% of all people with incident late onset Alzheimer's dementia who had a higher proportion with APOE ε4 alleles (45% compared with 34% for everyone with Alzheimer's dementia), a higher proportion with Braak stage ≥4 (indeed, 91% of this group had Braak stage ≥4), and a higher proportion with amyloid angiopathy. Furthermore, this group had eight of the IGAP SNVs with ORs ≥1.30 – and they were all in the risk direction (all shades of red in Table 3). Further analyses of this group are warranted.

The other subgroups appeared to be readily distinguishable from the group with isolated substantial memory impairment and in terms of the pattern of findings across the SNVs they were also distinguishable from each other. Larger sample sizes will be needed to make firmer conclusions about those groups.

4.2. Possible explanations for findings

One possible explanation for these findings is that the strategy we implemented to group people based on relative cognitive impairments works to identify biologically distinct Alzheimer's dementia subtypes. This explanation seems particularly well buttressed for the group with substantial relative impairments in memory, where *APOE* genotype, Braak stage, and seven IGAP SNVs had extreme ORs, all in the risk direction. The genetic data also suggest support for possible biological relevance for the group with substantial relative impairments in visuospatial functioning, where there were eleven IGAP SNVs with extreme ORs.

Another possibility is that our observations do not reflect biologically distinct groups and instead represent the play of chance. Replication in other samples will be very important to differentiate between these two possibilities.

4.3. Implications of findings

If these findings are replicated in other samples, they suggest that a non-invasive, widely-available technology – cognitive testing – may differentiate people with Alzheimer's disease into biologically relevant distinct subgroups. In the future, combinations of cognitive testing alongside other modalities such as structural MRI, CSF biofluids, or PET scans may be used to identify subgroups of people with similar biological processes that are distinct from those of people in other subgroups. Much work remains to be done; we are hopeful this work represents initial steps towards a personalized medicine approach to Alzheimer's dementia therapeutics.

4.4. Strengths and limitations

The ACT study includes a sample that reflects the demographic characteristics of the surrounding community. We chose to categorize people based on data at their initial Alzheimer's dementia diagnosis, so disease duration (and thus likely severity) should not vary much, though there may be differences in severity across subgroups even within this timeframe. The sample is limited in terms of ethnic heterogeneity; the genetic analyses are limited by design to people with European ancestry. The genetic findings are based on a relatively small number of study participants. Replication in additional study samples will be important. We were unable to evaluate differences in imaging parameters or in rates of cognitive change over time with the data available to us.

We evaluated heterogeneity among people with clinical Alzheimer's dementia based on NINCDS-ADRDA criteria. It has long been appreciated that there is an imperfect correlation between Alzheimer's pathology and diagnoses of dementia and Alzheimer's dementia, and that other forms of pathology such as vascular brain disease play important roles[29]. We found some differences in autopsy findings across cognitively-defined Alzheimer's dementia subgroups. Larger samples with autopsy data will be needed to more definitively investigate the roles disparate neurodegenerative conditions may play in the heterogeneity of clinical presentation.

The categorization scheme we developed borrows from principles that have been instrumental in clinical neuropsychology for many years, since it considers patterns of impairments, compared in this case to an individual's overall ability level (as opposed to their estimated premorbid ability). This approach successfully detected the individuals diagnosed with primary progressive aphasia and posterior cortical atrophy from the ACT study (see Box 1). These individuals can be considered "positive controls" to demonstrate the success of the categorization approach. The categorization scheme is based entirely on cognitive data, which is well tolerated and non-invasive. Most of our missing data were for visuospatial functioning; people with visual impairments severe enough that their visuospatial functioning cannot be assessed cannot be categorized using this approach. Furthermore, the visuospatial functioning domain was limited by the data we had available to form our composite scores. Future studies could investigate use of standard rather than modern psychometric approaches to determine subgroup membership.

We used theory-driven approaches to categorize people with late-onset Alzheimer's dementia rather than computer-driven approaches such as cluster analysis. Cluster analysis assigns people to categories that maximize distinctions between classes of people and result in categories that may reflect clinical experience but also may not. Subsequent research could compare our findings to those that would have been obtained with cluster analysis approaches.

4.5. Conclusions

Here we describe development and implementation of an approach to categorize people at the time of Alzheimer's dementia diagnosis based on patterns of memory, visuospatial functioning, language, and executive functioning. About half of those incident Alzheimer's

dementia had a single domain with a substantial relative impairment. Initial findings provide some support for the notion that these subgroups may be biologically distinct. Further work will be needed to replicate these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1

Illustration of cognitively defined subgroup procedures

We determined scores for memory, visuospatial functioning, language, and executive functioning. We determined each person's average across domains at dementia diagnosis. We determined differences from individual average scores.

Our first example case is a hypothetical individual:

	Memory	Visuospatial functioning	Language	Executive functioning
Scores	0.00	0.00	0.00	−1.00
Average	−0.25	−0.25	−0.25	−0.25
Difference	+0.25	+0.25	+0.25	−0.75

This person scored at the ACT average among people with Alzheimer's dementia for memory, visuospatial functioning, and language, and scored 1 SD below average for executive functioning (top row). This produces an average score of −0.25 (second row). The third row shows differences from average for each domain, with a difference of −0.75 for executive functioning, which would lead this person to be categorized in the substantial executive functioning impairment subgroup.

Our second example case was a real individual with scores as shown below:

	Memory	Visuospatial functioning	Language	Executive functioning
Scores	+1.02	−0.12	−1.02	−0.19
Average	−0.08	−0.08	−0.08	−0.08
Difference	+1.10	−0.04	−0.94	−0.11

This person's average score was −0.08. Her memory score was quite a bit better than this, while her language score was substantially worse (difference of −0.94 points). At the ACT consensus conference, she was diagnosed with primary progressive aphasia, a previously identified atypical Alzheimer's disease subtype characterized by intact memory and a substantial language impairment.

Our third example case was another real individual with scores as shown below:

	Memory	Visuospatial functioning	Language	Executive functioning
Scores	+2.00	+0.21	+1.39	+0.26
Average	+0.96	+0.96	+0.96	+0.96
Difference	+1.04	−0.75	+0.44	−0.70

This person's average score was +0.96. His memory score and language score were higher than his executive functioning and visuospatial functioning scores. He was diagnosed with posterior cortical atrophy, another previously identified atypical

Alzheimer's disease subtype characterized by intact memory and a substantial visuospatial functioning impairment.

These examples demonstrate procedures used to determine cognitively-defined subgroups of typical late-onset Alzheimer's dementia. The real examples show how these approaches work for one individual each with previously established atypical Alzheimer's disease subtypes.

Box 2

Performance of people with Alzheimer's dementia from the ACT study compared to published normative data

	Memory: Logical Memory II from the WMS-R[1]	Visuospatial Construction[2]	Language: Animal Fluency[2]	Executive functioning: Trails B[2]
Raw Score Norms, Previously Published				
Normal, 25th percentile	8 – 9	8.9	12.4	198
Normal, 50th percentile	1 1 – 13	10.2	15.3	150
Normal, 75th percentile	1 6	10.9	18.5	109
Mean (SD) from people from ACT with incident Alzheimer's dementia				
All with AD	1.7 (2.6)	8.8 (1.7)	10.5 (3.9)	231*
0 domains with relative impairment	1.4 (2.1)	8.9 (1.4)	10.4 (3.6)	257*
1 domain with relative impairment				
Memory	0.1 (0.7)	9.7 (1.2)	10.7 (4.0)	166 *
Visuospatial	2.7 (3.1)	7.2 (2.0)	12.0 (4.2)	230 *
Language	3.2 (3.2)	9.3 (1.4)	8.8 (3.5)	225 *
Executive functioning	3.6 (3.2)	9.2 (1.3)	8.8 (3.3)	300*
≥ 2 domains with relative impairment	3.5 (3.4)	8.0 (2.9)	10.8 (4.5)	300*

*Trails B is terminated at 5 minutes (300 seconds). The median and 25th percentile for everyone with Alzheimer's dementia and for each of the subgroups was 300 seconds (it was 296 seconds for the group with single domain – memory). For example, for everyone with Alzheimer's dementia, the 25th percentile was 300, and the median was 300, while the 75th percentile was 231. We thus show only the 75th percentile for people with Alzheimer's dementia from ACT.

This table shows published normative data and data from people with incident Alzheimer's dementia from the ACT study for one indicator from each domain. For the memory domain, scores for people with Alzheimer's dementia are substantially lower on Logical Memory II than published normative data for people over age 83 (median age 88)[1]. The group with substantial relative memory impairment had the very lowest performance, as expected. For the other three tests, we show published data from cognitively intact females aged 85–89 with >12 years education[2], which is the modal group for the ACT study. In the visuospatial functioning domain, construction was not especially impaired for people with Alzheimer's dementia compared with published normative data, with the exception of the people with substantial relative visuospatial functioning impairments. In the language domain, animal naming was substantially impaired compared with published normative data across all groups of people with Alzheimer's dementia, and most profoundly among those with substantial relative language impairments, but also among those with substantial relative executive functioning impairments. In the executive functioning domain, Trails B was 300 seconds (maximum value) for more than half of people with Alzheimer's dementia in the ACT study, and for at least three quarters of those in the isolated substantial executive functioning group and the group with more than 1 domain with a substantial impairment.

Research in Context

1. Systematic review: We reviewed PubMed literature sources on endophenotyping in the context of Alzheimer's dementia. We found many papers on fluid and neuroimaging biomarker strategies, but none that incorporated patterns of cognitive tests. We have contributed to the literature considering differences between memory and executive functioning among people with Alzheimer's dementia to isolate people with prominent executive dysfunction. We are not aware of studies that have also considered language and visuospatial functioning as well.
2. Interpretation: Our findings indicate that our cognitive subtyping strategy identified groups that had heterogeneous neuropathological findings and disparate relationships with genetic variants previously identified to be associated with risk for late-onset Alzheimer's dementia.
3. Future directions: Future research is needed to replicate these findings in other populations and determine whether a cognitive subtyping strategy may be useful to isolate biologically relevant subsets of people with Alzheimer's dementia and thus used as an endophenotyping strategy

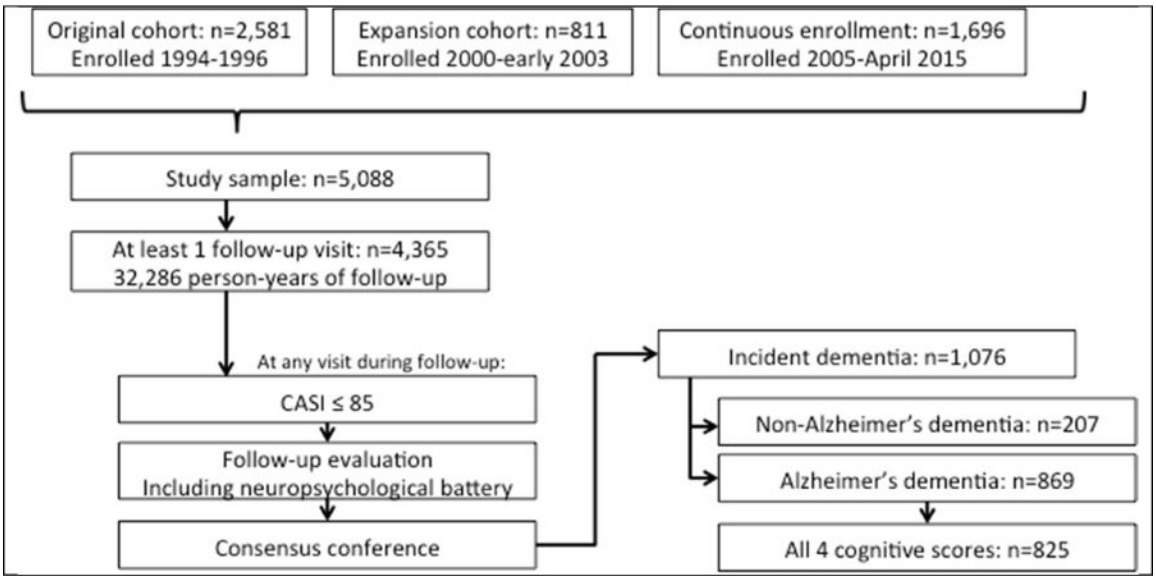

Figure 1.
Derivation of the analytic sample.

Table 1

Demographic characteristics, APOE genotype, and cognitive scores across cognitively-defined subgroups of 825 people with incident Alzheimer's dementia

Characteristics	Overall (N=825), mean (SD) or n (%)	No domain with relative impairment (N=393), mean (SD) or n (%)	Single domain impairment with relative				Multiple domains with relative impairments (N=30), mean (SD) or n (%)
			Memory (N=148), mean (SD) or n (%)	Visuospatial functioning (N=117), mean (SD) or n (%)	Language (N=71), mean (SD) or n (%)	Executive functioning (N=66), mean (SD) or n (%)	
Demographic characteristics							
Female sex	522 (63%)	248 (63%)	92 (62%)	77 (66%)	47 (66 %)	37 (56%)	21 (70%)
Enrollment age	77 (6)	77 (6)	76 (7)	78 (6)	77 (6)	76 (6)	78 (6)
Diagnosis age	86 (6)	86 (6)	85 (6)	86 (6)	86 (5)	85 (6)	87 (6)
Education	14 (3)	14 (3)	14 (3)	14 (3)	14 (3)	13 (3)	13 (4)
APOE genotype							
Any *APOE* ε4 alleles	243/711 (34%)	121/340 (36%)	60/130 (45%)	28/100 (28 %)	15/60 (25%)	13/58 (22%)	6/23 (26%)
Cognitive scores							
CASI	79 (9)	78 (10)	7 9 (8)	81 (8)	80 (7)	7 7 (8)	74 (1 1)
Average cognition	0.0 (0.7)	0.0 (0. 7)	0. 2 (0. 6)	0.0 (0. 8)	− 0.1 (0. 8)	− 0. 1 (0. 7)	− 0. 4 (0. 9)
Memory	0.0 (1.0) *	0.0 (0.8)	−0.9 (0.7)	0.6 (1.0)	0.3 (1.0)	0.5 (0.9)	0.3 (1.4)
Visuospatial functioning	0.0 (1.0) *	0.0 (0.8)	0.7 (0.7)	−1.2 (0.9)	0.4 (0.9)	0.2 (0.9)	−0.4 (1.4)
Language	0.0 (1.0) *	0.0 (0.8)	0.4 (0.9)	0.3 (0.9)	−1.1 (0.9)	0.1 (0.9)	−0.6 (1.4)
Executive functioning	0.0 (1.0) *	0.0 (0.9)	0.6 (0.8)	0.1 (1.0)	0.0 (0.9)	−1.1 (0.8)	−0.8 (1.6)

* Scores were standardized to have a mean of 0 and SD 1 among people with Alzheimer's disease who had all 4 scores.

Table 2

Autopsy findings for people with no dementia (n=294) and for people with clinical Alzheimer's dementia (n=180)*

		Alzheimer's disease						
				Single domain with relative impairments				
Autopsy finding	**No dementia (N=294), mean (SD) or n (%)**	**Total, all people with Alzheimer's disease (N=180), mean (SD) or n (%)**	**No domain with relative impairment (N=93), mean (SD) or n (%)**	**Memory (N=32), mean (SD) or n (%)**	**Visuospatial functioning (N=25), mean (SD) or n (%)**	**Language (N=12), mean (SD) or n (%)**	**Executive functioning (N=12), mean (SD) or n (%)**	**Multiple domains with relative impairments (N=6), mean (SD) or n (%)**
Alzheimer's pathology, amyloid angiopathy, hippocampal sclerosis								
Braak Stage, mean (SD)	2.8 (1.6)	4.4 (1.6)	4.3 (1.7)	5.1 (1.4)	4.2 (1.5)	4.4 (1.7)	4.4 (1.8)	4.2 (1.2)
Braak Stage ≥4, n (%)	66 (22%)	130 (72%)	63 (68%)	29 (91%)	16 (64%)	9 (75%)	9 (75%)	4 (67%)
CERAD level, mean (SD)	1.3 (1.1)	2.0 (1.1)	2.1 (1.0)	2.0 (1.2)	1.9 (1.1)	2.0 (1.2)	1.8 (1.3)	1.5 (1.0)
Sufficient AD*	71 (24%)	120 (67%)	62 (67%)	22 (67%)	17 (68%)	8 (67%)	8 (67%)	3 (50%)
Amyloid angiopathy	61/291 (21%)	67/179 (37%)	33 (35%)	16 (50%)	7/24 (29%)	5 (42%)	5 (42%)	1 (17%)
Hippocampal sclerosis	17/283 (6%)	25/176 (14%)	14 (15%)	5/50 (17%)	1/24 (4%)	2 (17%)	2 (17%)	1/5 (20%)
Lewy bodies								
Any Lewy bodies	41 (14%)	33/179 (18%)	19 (20%)	5 (16%)	4/24 (17%)	1 (8%)	3 (25%)	1 (17%)
Amygdala	31 / 275 (11%)	24/173 (14%)	14/90 (16%)	4/32 (13%)	4/23 (17%)	0 (0%)	2/11 (18%)	0 (0%)
Vascular brain injury								
Cystic infarcts	65/286 (23%)	73/179 (41%)	35/92 (38%)	12 (38%)	12 (48%)	7 (58%)	5 (42%)	2 (33%)
Microvascular infarcts								
Any microvascular infarct	100/293 (34%)	99/179 (55%)	50 (54%)	18 (56%)	14/24 (58%)	9 (75%)	6 (50%)	2 (33%)
Cortex	81/293 (28%)	80/179 (45%)	42 (45%)	15 (47%)	10/24 (42%)	7 (58%)	5 (42%)	1 (17%)
Deep	69/292 (24%)	72/178 (40%)	35/92 (38%)	10 (31%)	11/24 (46%)	8 (67%)	7 (58%)	1 (17%)

*Denominators are specified in column heads unless indicated. CERAD scores are 0 (none), 1 (sparse), 2 (moderate), 3 (frequent), or 4 (severe). "Sufficient AD" refers to having a Braak stage at least 3 and a CERAD level at least moderate.

Table 3

Genetic findings (see note for details)

rs number	Gene	MAF	Reported OR	Overall in ACT	No domain with relative deficits (n=217)	Single domain with relative deficits				Multiple domains with relative deficits (n=15)
						Memory (n=85)	Visuospatial functioning (n=65)	Language (n=38)	Executive functioning (n=37)	
rs11218343	*SORL1**	0.04	1.30	1.15	1.05	1.69	1.39	0.62	1.01	1.33
rs6733839	*BIN1*	0.41	1.22	1.10	1.25	1.02	1.17	1.09	0.78	0.70
rs6656401	*CR1*	0.20	1.18	1.29†	1.12	1.43†	1.65	1.49	0.98	1.80
rs9331896	*CLU**	0.38	1.16	0.85	0.85	1.14	0.71	0.71	1.12	0.59
rs4147929	*ABCA7*	*0.19*	1.15	1.17	1.30†	1.12	1.13	0.87	0.94	1.89
rs10792832	*PICALM**	0.36	1.15	1.11	1.14	1.36	0.96	1.03	1.20	0.55
rs17125944	*FERMT2*	0.09	1.14	1.25	1.16	1.26	1.39	0.67	1.30	1.83
rs7274581	*CASS4**	0.08	1.14	1.07	1.06	1.52	1.67	0.96	0.59	0.46
rs983392	*MS4A6A**	0.40	1.11	1.08	1.02	1.39	1.12	1.09	0.84	1.09
rs11771145	*EPHA1**	0.34	1.11	1.01	0.95	1.32	0.76	0.82	1.45	0.95
rs9271192	*HLA-DRB5-HLA-DRB1*	0.28	1.11	0.86	0.89	0.93	1.07	0.65	0.55†	0.64
rs28834970	*PTK2B*	0.37	1.10	1.24†	1.28†	1.22	0.82	1.49	1.47	1.45
rs10948363	*CD2AP*	0.27	1.10	1.19	1.18	1.15	1.28	1.66†	1.12	0.92
rs1476679	*ZCWPW1**	0.29	1.10	1.03	1.11	1.31	0.98	0.57†	0.80	1.44
rs10498633	*SLC24A4-RIN3**	0.22	1.10	1.23†	1.31†	1.14	1.44	1.38	1.19	0.99
rs35349669	*INPP5D*	0.49	1.08	1.12	1.05	1.10	0.94	1.26	1.31	1.44
rs10838725	*CELF1*	0.32	1.08	1.02	0.97	1.33	0.71	0.98	1.05	1.04
rs2718058	*NME8*	0.37	1.08	1.00	0.90	1.18	1.26	0.66	1.20	0.62
rs190982	*MEF2C**	0.41	1.08	1.22†	1.23	1.27	1.23	1.14	0.96	1.41
rs3865444	*CD33**	0.31	1.06	1.18	1.33†	0.89	1.39	0.95	0.98	1.65

The first column shows the rs number for the 20 SNVs reported in Lambert et al. (2014) to be associated with late-onset Alzheimer's dementia. The second column shows the closest gene to the tag SNV. The third column shows the minor allele frequency (MAF) reported in Lambert et al. (2014). The fourth column shows the odds ratio (OR) reported in Lambert et al. (2014). Some minor alleles were protective; we took the inverse of these protective odds ratios (marked with*) such that each odds ratio shown here is in the risk direction. We sorted SNVs in descending order of their odds ratios. The fifth column shows the overall odds ratio for the ACT study. SNVs with a single dagger (†) had a nominal p<0.05 in the ACT study. The next six columns show odds ratios for each subgroup in the ACT study, each compared with cognitively normal elderly controls. The color coding scheme is increasingly red for successively higher odds ratios (1.30–1.49 light pink, 1.50–1.74 medium pink, 1.75–1.99 dark pink, ≥2.00 dark red) and increasingly blue for successively lower odds ratios (0.77–0.67 turquoise, 0.66–0.58 light blue, 0.57–0.51 medium blue; <0.5, dark blue). We chose to mark ORs greater than 1.30 (or less than 1/1.30~0.77) as that was the size of the largest OR reported in Lambert et al. (2014).

1. Ivnik RJ, Malec JF, Smith GE, et al. Mayo's older americans normative studies: WMS-R norms for ages 56 to 94. *Clinical Neuropsychologist.* 1992;6(sup001):49–82.

2. Beeri MS, Schmeidler J, Sano M, et al. Age, gender, and education norms on the CERAD neuropsychological battery in the oldest old. *Neurology.* 2006;67(6):1006–1010.