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ABSTRACT

Objective To investigate whether some patients with very mild Alzheimer's disease (AD) demonstrate disproportionate executive dysfunction relative to amnesia and how this relates to functional impairment in daily life, future clinical decline, APOE genotype and regional cortical thickness measured from MRI scan data.

Methods The Alzheimer's Disease Neuroimaging Initiative dataset was interrogated for a primary sample of patients with very mild AD dementia (n=100) and a secondary confirmatory sample of patients with mild cognitive impairment (n=396). An executive predominant subgroup was defined as having executive performance ≥2 SDs worse than memory performance and a memory predominant subgroup was defined conversely. A priori regions of interest from a previous study of an AD patient sample were used to obtain cortical thickness measures.

Results Despite equivalent global measures of impairment (Mini-Mental State Examination, Clinical Dementia Rating (CDR) Sum of Boxes), executive predominant patients (n=88) were more impaired on other executive measures and in the CDR Judgement and Problem Solving box ($p<0.005$) while memory predominant patients (n=56) were more impaired on other memory measures ($p<0.05$). The APOE-ϵ4 allele was much more frequent in the memory predominant subgroup ($p<0.0001$). Frontoparietal cortical regions were thinner in the executive predominant group than in the memory predominant group ($p<0.05$).

Conclusions A dysexecutive clinical phenotype of very mild AD is not rare and is associated with more problem solving difficulties and possibly more rapid progression compared with patients with a predominant amnesic phenotype. Executive predominant AD may reflect an alternative underlying pathophysiology related to genetic status, reflected in more prominent pathological alterations in frontoparietal regions subserving executive function. These findings, which deserve further investigation, may have implications for diagnosis, prognostication, monitoring and related issues involved in clinical research and care.

The dementia of Alzheimer's disease (AD) is diagnosed when an individual loses independent functioning as a result of impairments in memory and at least one or more other domains of cognition.[1 2] These symptoms are a reflection of the loss of function of brain systems for memory, executive function, visuospatial function, language, praxis and other abilities, and result, at least in part, from the accrual of neuropathology in multiple regions of the cerebral cortex.[3 4] Although current diagnostic criteria—including traditional and recent draft criteria[5]—require memory impairment as a feature of 'typical' AD, clinical experience and research indicate that there are 'atypical' forms of AD in which the most salient impairments are in non-memory domains.

It has been known for more than two decades that there can be patients who appear to have AD but who exhibit executive dysfunction that is disproportionate to the level of amnesia.[6–8] Investigators have identified cases of AD in which the major feature is executive dysfunction who are pathologically confirmed to have AD but with relatively prominent frontal pathology.[9] These findings have recently been extended to the identification of a dysexecutive form of mild cognitive impairment (MCI).[10]

Although these seminal observations are important, numerous questions remain. It is not clear how common a predominantly dysexecutive phenotype of AD is early in the course of the illness, and there has been little study of its characteristics with respect to functional impairment in daily life. Furthermore, although the previously mentioned MCI study reported valuable findings, there has been essentially no study of the genetic and neuroanatomical characteristics of a dysexecutive form of AD in a large sample of patients.

In the present study, we set out to confirm and extend ideas related to the clinical characteristics of a dysexecutive phenotype of AD early in the illness course. The hypothesis was that there are individuals with early AD who have more prominent executive dysfunction than memory impairment and that this is associated with distinct clinical and biological characteristics. We first took an exploratory approach, employing data from patients with very mild AD dementia (Clinical Dementia Rating (CDR)=0.5, probable AD diagnosis), using two widely available neuropsychological tests to identify a subgroup with disproportionate executive dysfunction (executive predominant subgroup) and a subgroup with disproportionate memory loss (memory predominant subgroup). We investigated the replicability of these findings in an MCI patient group (CDR=0.5, MCI diagnosis), their generalisability to other psychometric tests and their relationship to impairments in daily life and future clinical decline. Finally, we investigated the biological characteristics of these subgroups by

comparing APOE genotype frequency and quantifying neuroanatomical abnormalities presumably associated with the localisation and severity of AD neuropathology. For the anatomical analysis, a priori regions of interest obtained from a previous study were used to test the hypothesis that the dysexecutive predominant subgroup would exhibit more prominent thinning within frontoparietal regions considered to be part of large scale networks for executive control and complex attention.

PARTICIPANTS AND METHODS

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). The 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 non-profit organisations, 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 MCI and early AD.

The ADNI dataset was queried for baseline clinical data for subjects with a clinical diagnosis of MCI or AD with very mild impairment (CDR=0.5) and also for subjects diagnosed as normal (n=229, mean age 75.9 years).

Two tests were used to define the subgroups of interest: the Trail Making Test and Alzheimer's Disease Assessment Scale-Cognitive subscale Word Recognition. This 'psychometric dissociation' approach was used because it is easily replicable in a standardised fashion using readily available tests and as such could be used to screen large cohorts. To obtain a measure of executive function (sequencing) from Trails, part A time was subtracted from part B time. To obtain a measure of recognition memory discriminability, d prime was calculated in a standard fashion based on classic signal detection theory[11]: $d' = Z_{FA} - Z_{Hits}$ where Z_{FA} and Z_{Hits} are Z scores reflecting the proportion of false alarms and hits, respectively. Additionally, because d' is undefined when either proportion is 0 or 1, we used standard formulae to convert these values: Hits=(#Hits+0.5)/(#studied items+1) and FA=(#FA+0.5)/(#unstudied items+1).

Neuropsychological data from normal controls were used to generate a mean and SD for each test that was then used to derive Z scores for each patient. Patients were then classified into the 'executive predominant' subgroup if the executive measure was ≥2 SDs below the memory measure and conversely into the 'memory predominant' subgroup.

To investigate the generalisability and consistency of these clinical subgroup distinctions, two identical factor analyses were performed—one for MCI and one for AD patient groups—using the following neuropsychological variables not used in subgroup definitions: Boston Naming Test, Animal Fluency, Vegetable Fluency, Auditory–Verbal Learning Test (AVLT) Discriminability, AVLT Delayed Free Recall, AVLT Total Learning, Digit Symbol, Digit Span Forward and Digit Span Backward. Factor analyses were performed using a principal components analysis (Varimax rotation, scores generated using regression method). Given that the absolute scores on these measures are difficult to interpret, Cohen's d effect size measures were used to compare the magnitude of subgroup differences.

Using ANOVA, comparisons were made between the subgroups with respect to baseline CDR box scores and 2 year decline in CDR Sum of Boxes scores. Biological differences between subgroups were explored by comparing APOE genotype frequencies (χ^2 analysis). This analysis was further refined by restricting cases to only those with CSF A-beta values consistent with those of autopsy proven AD (<192).[12]

Finally, cortical thickness measures were obtained from MRI scan data in the very mild AD patient group using a previously published hypothesis driven analytical approach.[13 14] Very briefly, the multiple T1 acquisitions for each participant were motion corrected and averaged. The resulting averaged volume was used to segment cerebral white matter and multiple subcortical grey matter and ventricular regions and to estimate the location of the gray/white boundary. Topological defects in the gray/white boundary were corrected, and this gray/white boundary was used as the starting point for a deformable surface algorithm designed to find the pial surface with submillimetre precision. Cortical thickness measurements were obtained by calculating the distance between those surfaces at each of approximately 160 000 points (per hemisphere) across the cortical mantle. Mean thickness of each individual subject's entire cerebral cortex was then calculated. The surface representing the gray/white border was 'inflated,' differences among individuals in the depth of gyri and sulci were normalised and each subject's reconstructed brain was then morphed and registered to an average spherical surface representation that optimally aligns sulcal and gyral features across participants. Thickness measures were then mapped to the inflated surface of each participant's reconstructed brain and the data were smoothed on the surface using an iterative nearest neighbour averaging procedure (n=100 iterations). Data were then resampled for participants into a common spherical coordinate system. The procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy, while minimising geometric distortion, resulting in a mean measure of cortical thickness for each group at each point on the reconstructed surface. The Freesurfer software used to analyse and visualise data in this study is freely available (http://surfer.nmr.mgh.harvard.edu).

This analysis provides cortical thickness measurements from nine regions of interest (ROIs) previously determined to be thinner in a separate large sample of AD patients compared with similarly aged controls, which are then used for hypothesis testing, as previously described in detail.[13] In this study, we focused on a comparison of the superior frontal gyrus, middle frontal gyrus (dorsal bank of the inferior frontal sulcus, called the inferior frontal sulcus in previous publications), supramarginal gyrus, superior parietal lobule and medial temporal lobe (MTL), hypothesising that the executive predominant subgroup would exhibit greater thinning in lateral frontoparietal regions while the memory predominant subgroup would exhibit greater thinning in the MTL. Hippocampal volume (adjusted for intracranial volume; both measured using the automated segmentation algorithms Freesurfer) was also hypothesised to be smaller in the memory predominant subgroup. As previously,[13] we transformed these measures to Z scores using the mean/SD of the normal control group for each ROI. All statistical analyses were performed using SPSS 16.0.

RESULTS

Of the 100 patients in the very mild AD patient group, 27 were classified as executive predominant and 12 as memory predominant. Of the 395 patients in the MCI patient group, 61 were classified as executive predominant and 44 as memory predominant. For both AD and MCI patient groups, the two subgroups did not differ in age, education, gender or Mini-Mental State Examination score.

Demographic and clinical characteristics of the participants are presented in table 1, and figure 1 illustrates discrepancies in memory and executive performance.

In each of these clinical subgroups—executive predominant very mild AD and executive predominant MCI—performance on the sequencing task was impaired at a strikingly disproportionate level relative to the memory predominant subgroups. In the executive AD group, the sequencing score was −4.2±0.9 while in the memory AD group, performance was 0.94±1.9 SD above the control mean. The same was true for the executive predominant MCI group, with a score of −3.7±1.3, while in the memory predominant MCI group the score was 0.70±1.2.

The memory measure was less disproportionately impaired between the two subgroups, partly given the expected greater average memory impairment in all groups based on the original ADNI diagnostic criteria. In the memory predominant MCI subgroup, memory score was −2.19±0.83, while in the executive predominant MCI group the score was −0.52±1.1. Similarly, in the memory predominant AD group, the memory score was −2.49±0.7 compared with that in the executive predominant AD group (score −1.0±0.9).

Factor analysis of other neuropsychological measures

In the AD patient group, the psychometric factor analysis identified three factors that explained 63% of the variance. The factors were interpreted as representing Lexical Retrieval and Executive Function (Boston Naming Test, Animal Fluency, Vegetable Fluency), Episodic Memory (AVLT Discriminability, AVLT Delayed Free Recall, AVLT Total Learning) and Processing Speed/Working Memory (Digit Symbol, Digit Span Forward, Digit Span Backward).

The executive predominant AD subgroup performed substantially worse than the memory predominant subgroup on the Lexical/Executive factor (Cohen's d effect size comparing the two subgroup means=0.96, $p<0.05$) but substantially better on the Episodic Memory factor (Cohen's d=0.91, $p<0.05$). There was no difference on the Processing Speed/Working Memory factor ($p=0.25$).

The MCI group showed remarkably similar results. A factor analysis using the same measures revealed three factors that explained 67% of the variance. In this independent analysis, the factors identified were identical to those above with the exception that Digit Symbol loaded on factor 1 (Lexical/Executive).

The executive predominant MCI subgroup performed worse than the memory predominant subgroup on the Lexical/Executive factor (Cohen's d=0.59, $p<0.05$) and on the Working Memory factor (Cohen's d=0.72, $p<0.05$) but better on the Episodic Memory factor (Cohen's d=0.40, $p<0.05$).

Relationship to impairment in daily life

Given the remarkable similarity in many of the measures identified above, additional analyses of functional measures were conducted by combining the AD and MCI subjects into a single group since the focus was on disproportionate impairments between the executive predominant and memory predominant subgroups.

With respect to symptom severity in daily life, although the overall CDR Sum of Boxes measure was similar between the two subgroups at baseline (2.2±1.1; 2.0±1.1; $p=0.3$), the executive predominant subgroup was more impaired in the Judgement and Problem Solving box than the memory predominant subgroup (0.55±0.3; 0.38±0.3; $p<0.005$) (figure 2). Other CDR box measures did not differ between the subgroups. There were no differences between the groups on total Functional Assessment Questionnaire or subscores within the Functional Assessment Questionnaire.

Two year follow-up data were available for 63 of the MCI and AD patients (44% of the MCI and 42% of the AD patients in the present sample, nearly equally split among memory and executive predominant subgroups), indicating a trend towards more rapid decline in CDR Sum of Boxes in the executive predominant group (3.1±3.2) than in the memory predominant group (1.8±1.9, $p=0.07$) (figure 2).

The effect sizes of these findings were similar when the two diagnostic groups (MCI and AD) were analysed separately.

Differences in APOE genotype frequency

The APOE-ϵ4 allele was over-represented in memory predominant (61% carriers) relative to executive predominant (49% carriers) subgroups ($\chi^2=7.1$, $p<0.0001$). To determine whether this disparity might be related to the presence of non-AD pathologies, the entire subject pool (CDR 0.5 MCI and CDR 0.5 AD with a predominant dysexecutive or amnesic phenotype) was restricted based on a CSF A-beta level of <192, consistent with AD pathophysiology, resulting in 24 memory predominant and 41 executive predominant predominant patients (78% of MCI patients and 87% of AD patients with CSF samples available, proportions of memory and executive predominant subgroups were nearly identical). Of those 65 individuals, the APOE-ϵ4 allele was still over-represented in the memory predominant (79% carriers) compared with the executive predominant (44% carriers) subgroups ($\chi^2=7.7$, $p<0.0001$) (figure 3).

Differences in regional cortical thickness

The executive predominant subgroup exhibited more prominent thinning than the memory predominant subgroup in the superior parietal and superior frontal ROIs ($p<0.05$), despite a similar magnitude of thinning in the MTL and other ROIs (figure 4). In the executive predominant subgroup, these regions had respective Z scores of −1 and −0.9 while in the memory predominant subgroup their Z scores were −0.1 and 0. Interestingly, hippocampal volume demonstrated a difference in absolute magnitude in the opposite direction with Z scores of −1.6 in the memory predominant subgroup and −1.1 in the executive predominant

Table 1 Demographic and clinical characteristics of the participants

Group	N	Age (years)	Gender (M/F)	Education (years)	MMSE	CDR Sum of boxes	FAQ
Executive predominant MCI	61	74.8±8.0	36/25	14.8±3.5	26.4±1.7*	1.8±0.9*	4.0±4.4*
Memory predominant MCI	44	74.6±8.4	27/17	15.7±3.1	27.0±1.9*	1.7±0.9*	3.6±4.5*
Executive predominant AD	27	75.7±8.8	16/11	14.4±3.8	23.7±2.2* †	3.2±1.0* †	11.1±6.4* †
Memory predominant AD	12	75.0±6.2	5/7	15.5±3.4	24.5±1.8* †	3.4±0.8* †	10.8±4.3* †

Values are mean±SD.
AD, Alzheimer's disease; CDR, Clinical Dementia Rating; FAQ, Functional Assessment Questionnaire; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.
*$p<0.001$ compared with normal controls.
†$p<0.001$ compared with MCI.

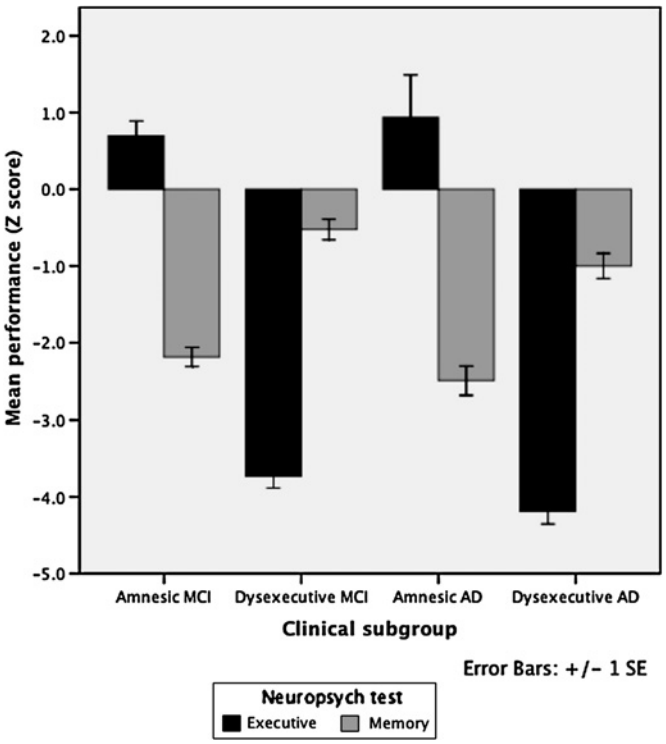

Figure 1 Distinct phenotypes of Alzheimer's disease (AD). An executive predominant AD subgroup can be identified and is also present in mild cognitive impairment (MCI) with relatively prominent executive dysfunction and much less impaired memory. A memory predominant AD subgroup can be identified and is also present in MCI with relatively prominent memory loss and unimpaired executive function. Performance data shown here are from tests used to define the groups. Error bars depict 1 SEM.

subgroup, but this was not statistically significant ($p>0.1$). The other regions did not demonstrate clear effects.

DISCUSSION

Patients with AD, while typically conceptualised as having an illness primarily of episodic memory, may manifest more prominent dysfunction in other cognitive domains, sometimes as the most salient feature of the illness. Threads of clinical research going back two decades have investigated the clinical heterogeneity of AD and the possibility of consistent clinical subtypes.[7 9 15] Based on our own experience having seen individuals with such disparate forms of AD, we sought here to compare the characteristics of very mild AD patients with disproportionate executive dysfunction to those with predominant amnesia. We found that the executive predominant and memory predominant subgroups were reliably identifiable in two separate patient groups in the ADNI sample (MCI and AD, both CDR 0.5), indicating that even at a very mild stage of the illness such distinct clinical subtypes are not uncommon, consistent with a previous investigation of dysexecutive MCI.[10] The subgroups were defined on the basis of performance on two neuropsychological tests but exhibited consistent generalisable deficits in these cognitive domains on multiple tests (separate from those used to define the subgroups). Furthermore, the executive predominant subgroup was more impaired than the memory predominant subgroup in daily life with respect to judgement and problem solving and showed a trend towards more rapid overall 2 year clinical decline. In addition to investigating these clinical characteristics, as first steps towards exploring biological differences between these subgroups, we found that the APOE-ε4 allele was considerably over-represented in the memory predominant subgroup (nearly twice as frequent) compared with the executive predominant subgroup, and that the executive predominant subgroup exhibited more prominent cortical atrophy in lateral frontoparietal regions than the memory predominant subgroup.

Although executive, language, visuospatial or behavioural symptoms may dominate the clinical picture of atypical forms of AD, executive dysfunction may not stand out as much as a primary feature because it colours performance in many other domains, particularly memory. Individuals with prominent executive dysfunction may appear to be globally impaired on neuropsychological tests although careful probing of cognitive domains using tasks with reduced executive demand may indicate relative preservation of memory, language or visuospatial function. For example, deficits in free recall, which have been heavily employed as indicators of amnesia in AD research,[16] clearly reflect not only memory but also executive and lexical search processes involved in retrieval.[17 18] For this reason, we chose to operationalise the definition of amnesia in this study using a recognition discriminability index which represents the

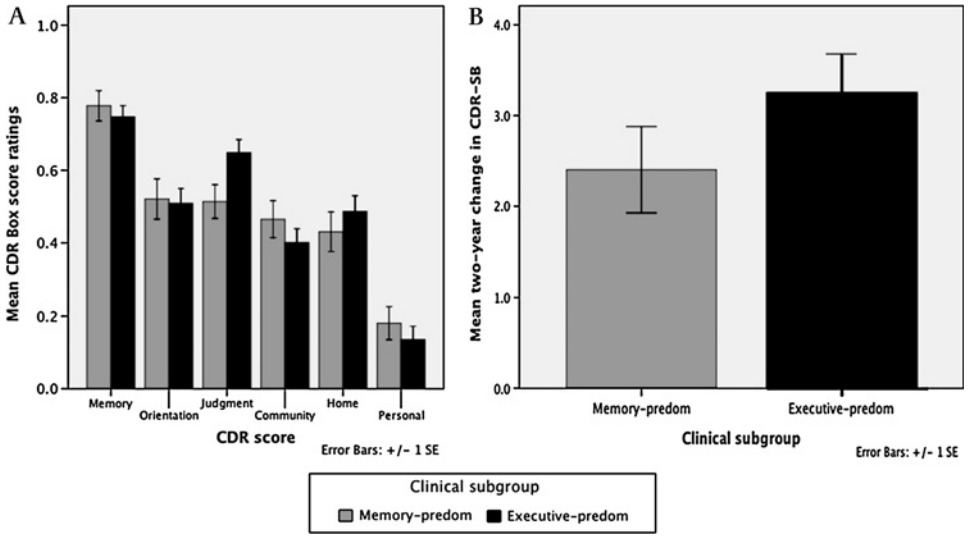

Figure 2 Clinical ratings of subgroups at baseline and follow-up. (A) Baseline Clinical Dementia Rating (CDR) Box score ratings in clinical subgroups. The executive predominant subgroup is more impaired in Judgement and Problem Solving than the memory predominant subgroup ($p<0.005$). (B) Change in CDR Sum of Boxes score in the two subgroups at the 2 year follow-up, demonstrating a trend towards more rapid progression in the executive predominant subgroup ($p=0.07$).

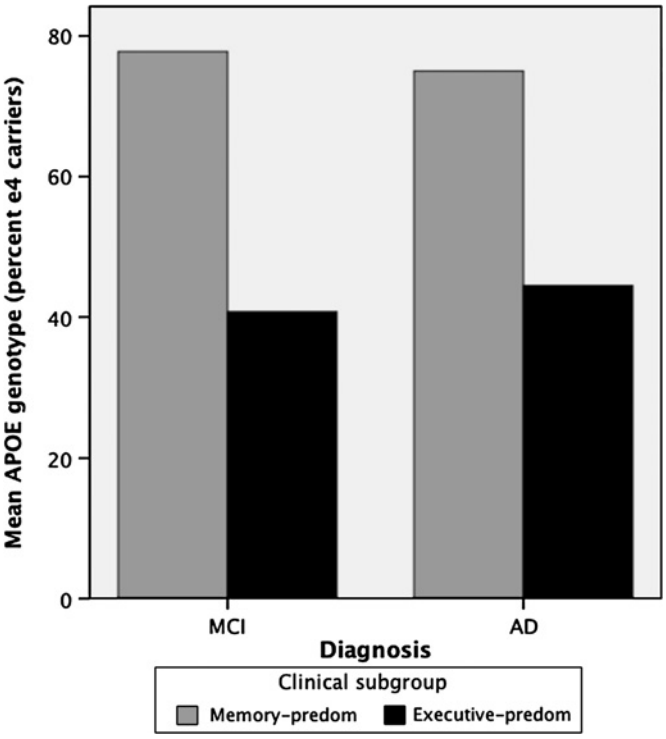

Figure 3 Per cent APOE-ϵ4 carriers in the memory predominant subgroups is nearly double that of the executive predominant subgroups ($p<0.0001$ in each diagnostic group), with remarkably similar values in very mild Alzheimer's disease (AD) dementia patients and in those with mild cognitive impairment (MCI) with a CSF A-beta profile similar to that of autopsy proven AD.

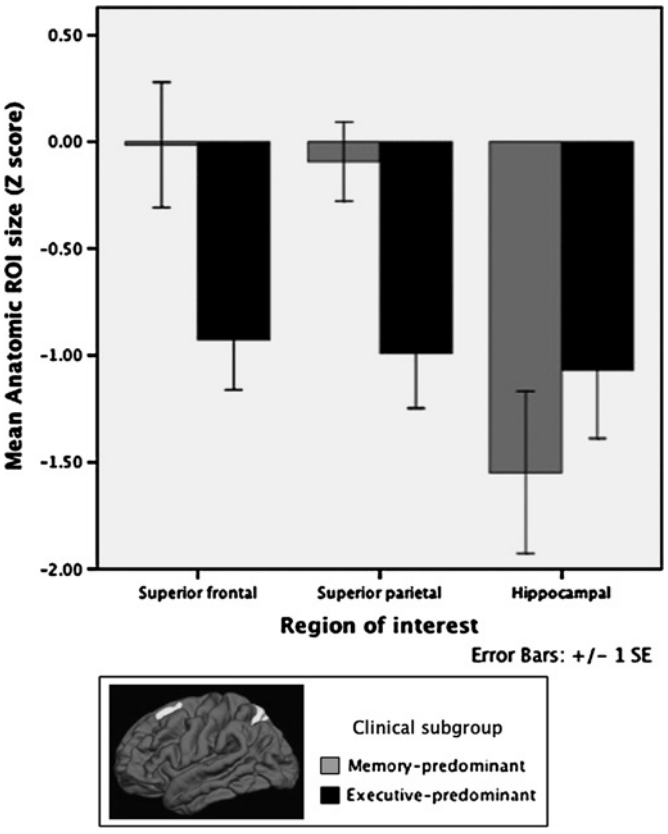

Figure 4 Magnitude of regional atrophy in the subgroups. Despite a trend towards slightly lesser hippocampal atrophy, the executive predominant subgroup shows much more prominent thinning in the superior frontal and superior parietal cortices than the memory predominant subgroup ($p<0.05$). Hippocampal volumes were suggestive of an opposite effect but not statistically significant. Brain image shows localisation of frontal and parietal regions of interest (ROI).

individual's ability to correctly recognise previously encountered information as old while identifying information not previously encountered as new. This type of memory task is usually considered to be subserved by the temporolimbic episodic memory system(s) and to be low with respect to demands on executive function, as reflected by relative sparing of performance in frontal lesion patients.[19] In contrast, executive function was operationalised using the letter–number sequencing task of the Trail Making Test, adjusted for speed on the rote number sequencing task. This type of executive task is thought to be subserved by frontoparietal executive control systems.[20] We employed an approach using two individual, widely used tests because we hope that this will enable the efficient investigation of this issue in other large samples in which similar tests are used, and because future studies could add these two tests with little additional burden.

Based on these two distinct psychometric performance measures, we identified very mild AD patients with much more prominent (difference of at least 2 SDs) executive dysfunction than memory impairment and others with much more impaired memory than executive function. We specifically did not require normal performance in either domain, as has been done previously,[10] because this investigation was focused on the predominance of dysfunction within a particular cognitive domain in patients who have multiple cognitive deficits rather than impairment solely within a single domain. We investigated the generalisability of these findings in two ways. Firstly, the executive predominant and memory predominant clinical subgroups were also identified in the MCI patient sample. Secondly, factor analyses were performed separately in the AD and MCI patient groups on other psychometric tasks not used to define the clinical subgroups and identified three similar factors representing Lexical/Executive function, Episodic Memory and Processing Speed/Working Memory. In both the MCI and AD patient groups, the phenotypes generalised to these factors with the executive predominant subgroups of both MCI and AD patient groups performing worse on these other measures of Lexical/Executive function and the memory predominant subgroups both performing worse on other measures of Episodic Memory. These findings are similar to those reported previously for dysexecutive MCI patient subgroups[10] and for patients with mild to moderate AD,[7] but their replication in two separate samples in the present study support the idea that they are broadly generalisable.

One might question our classification of MCI patients from the ADNI cohort as having a dysexecutive phenotype as all patients were diagnosed with traditional amnestic MCI[21] for inclusion in the cohort. However, just as with mild clinical AD, these patients may still have disproportionate executive impairment despite concomitant amnesia. Furthermore, a free recall memory measure (Wechsler Memory Scale Logical Memory II) was used to operationalise objective memory impairment to qualify for the a-MCI diagnosis. Thus it is possible that those with prominent executive impairment displayed free recall deficits at least partly on this basis rather than due to the loss of integrity of temporolimbic structures. Indeed, this group performed less than 0.5 SDs below that of healthy controls on the recognition memory measure,

suggesting a relative preservation of the mnemonic aspects of episodic memory.

In addition to psychometric differences, the executive predominant subgroup exhibited greater impairment in the CDR Judgement and Problem Solving box, an indication of greater executive dysfunction in daily life. There was a trend towards slightly more impairment in the CDR Memory box in the memory predominant subgroup (figure 2A). Comparable results were reported previously[10] with respect to more prominent executive dysfunction in daily life in the dysexecutive MCI subgroup, as measured by the Dysexecutive Questionnaire.[22] Furthermore, in the present study, the rate of clinical decline, as indicated by the 2 year change in CDR Sum of Boxes was slightly higher (trend level effect) in the executive predominant subgroup than in the memory predominant subgroup. To our knowledge, such results relating to prognostic implications of a dysexecutive AD phenotype have not been previously reported.

With respect to the potential biological underpinnings of these subtypes, we identified a much higher (nearly double) frequency of the APOE-ϵ4 allele in the memory predominant subgroup compared with the executive predominant subgroup. This was also observed previously by Pa *et al* with 52% ϵ4 carrier frequency in their amnesic MCI subgroup and 37% carrier frequency in their dysexecutive subgroup. However, one criticism of their finding, as they point out in the discussion, is that some of their dysexecutive MCI group may not have underlying AD pathology which would effectively dilute the carrier frequency. The fact that we found similar results limited to patients with a CSF profile consistent with AD mitigates against this argument.

It is possible that APOE genotype modulates the clinical phenotype of AD through its effects on large scale memory networks of the brain.[23] For example, ϵ4 carriers have been found to have greater memory impairment and medial temporal atrophy than non-carriers.[24] Conversely, a recent study found greater orbitofrontal and dorsal frontoparietal atrophy in non-carriers.[25] As with our finding in AD patients with a prominant dysexecutive phenotype, other atypical presentations of AD also appear associated with a lower ϵ4 carrier status, suggesting that this gene may be less important as a risk factor for atypical phenotypes.[26]

With respect to underlying anatomical features, we found that our executive predominant AD subgroup demonstrated relatively greater dorsal frontoparietal cortical thinning than the memory predominant subgroup, who demonstrated a trend towards more prominent hippocampal atrophy. These dorsal frontoparietal regions are critical nodes in the 'dorsal attention network,' commonly activated in functional neuroimaging studies of working memory and attention.[27 28] These findings regarding differences between the two subgroups are similar to those hypothesised previously but not found in the dysexecutive MCI study.[10] Neuroanatomical differences between subgroups of patients with AD or other neurodegenerative diseases may be difficult to identify because they may be subtle, thus requiring a hypothesis driven approach such as that employed here.

Some limitations of this analysis include the focus on clinically probable AD and MCI, which likely includes individuals with non-Alzheimer pathologies. However, given that the emphasis of this analysis is on clinical phenotyping and that it was performed in the ADNI cohort, in which uniform and fairly strict clinical criteria were implemented, the results are potentially broadly generalisable to many patients with similar clinical characteristics. Future analyses will focus further on determining whether similar clinical subgroups can be identified in individuals with in vivo evidence of amyloid binding and similar characteristics that increase the likelihood of AD pathology. Another limitation is the focus on psychometric definitions of executive versus memory dysfunction; it would be ideal to perform such subgrouping by including the characteristics and severity of symptoms in daily life as part of the definition of the subgroup. A paucity of this type of data is being prospectively collected as part of ADNI, and the addition of instruments such as the dysexecutive questionnaire for prospective data collection would be valuable for future studies. The finding reported here regarding slightly more impaired judgement and problem solving suggests that instruments focusing on these issues will probably yield relevant results. Another limitation of the present analysis relates to the possibility of differential effects related to cerebrovascular disease or risk factors; although ADNI inclusion criteria require a Hachinski Ischaemic Scale score ≤4, which curtails the presence of significant vascular disease or risk factors, it would be of interest to investigate whether differences in the phenotypes or rates of progression reported here may relate to white matter hyperintensities or cerebrovascular risk factors.

Further investigations focused on morphometric and functional brain measures, in addition to neuropathology, will surely contribute in important ways to advancing our knowledge of the putative biological mechanisms of clinical phenotypic heterogeneity in AD. Refined data on AD clinical phenotypes will likely be valuable not only for clinical practice with respect to differential diagnosis and prognostication but also for recruitment of more homogenous patient groups for clinical trials of potential therapeutic interventions.

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Competing interests None.

Ethics approval This study was conducted with the approval of the multiple institutions.

Contributors Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators is available at http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Citation.shtml. BCD and DAW performed all statistical analyses.

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