THE LANCET Neurology

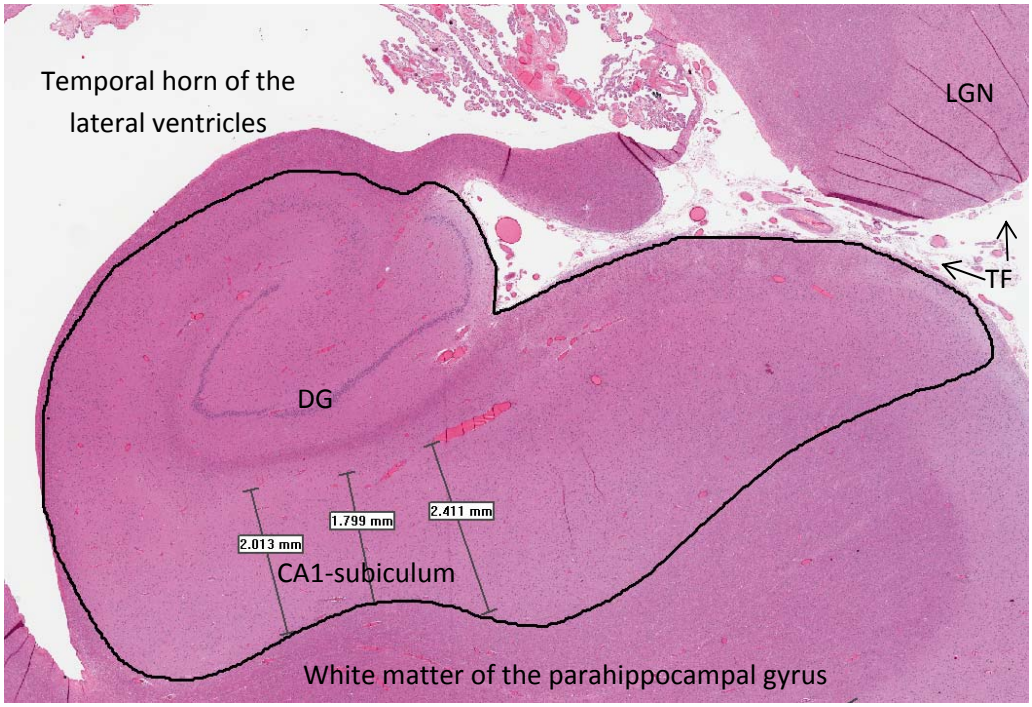
Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Murray ME, Graff-Radford NR, Ross OA, et al. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurol* 2011; published online July 28. DOI:10.1016/S1474-4422(11)70156-9.

Supplemental Figure 1.

Hippocampal area was quantified for each case by manually tracing the posterior hippocampus at the level of the lateral geniculate nucleus (LGN) using standard landmarks to define the perimeter. The thickness of the CA1-subiculum border was measured below the dentate gyrus (DG) and defined in triplicate to average any differences along its length.



Abbreviations: LGN – lateral geniculate nucleus, DG – dentate gyrus, CA1- cornu Ammonis, TF – transverse fissure of Bichat.

Supplemental Table 1.

There was no difference in the distribution of AD subtypes depending upon the referral source.

Referral source	Hippocampal sparing	Typical AD	Limbic predominant	
ADC	15 (10%)	113 (73%)	27 (17%)	
ADI	64 (11%)	441 (75%)	84 (14%)	
Consults	18 (21%)	49 (75%)	6 (5%)	
SPSP	5 (17%)	22 (75%)	2 (7%)	χ^2; p = 0.176
EAS	0 (0%)	16 (76%)	5 (24%)	
PDC	0 (0%)	17 (77%)	5 (23%)	
FADRC	1 (13%)	7 (88%)	0 (0%)	

ADC = Mayo Clinic Jacksonville Memory Disorder Clinic, ADI= State of Florida Alzheimer Disease Initiative; Consults=hospital consults; SPSP=Society for Progressive Supranuclear Palsy brain bank; EAS=Einstein Aging Study; PDC=Mayo Clinic Jacksonville Movement Disorder Clinic; FADRC= Florida Alzheimer's Disease Research Center

Supplemental Table 2.

The patients from sources not specializing in aging and dementia (PDC, SPSP, consults) showed similar distribution of age at death for AD subtypes (only medians are reported, given the smaller sample size).

Referral source	Hippocampal sparing	Typical AD	Limbic predominant
Consults	71	81	91
SPSP	69	73	72
PDC	0	83	88
All non-AD study sources	69	80	88

Consults=hospital consults; SPSP=Society for Progressive Supranuclear Palsy brain bank; PDC=Mayo Clinic Jacksonville Movement Disorder Clinic

Supplemental Table 3.

The *MAPT* finding remained significant even after excluding cases from parkinsonian referral sources (ie SPSP and PDC).

MAPT	**H1H1**	**non-H1H1**	
Hippocampal sparing	21 (46%)	25 (54%)	
Typical	190 (60%)	126 (40%)	χ^2; p = 0.0236
Limbic predominant	52 (69%)	23 (31%)	

Supplemental Table 4.

A Chi-square analysis was run on 775 cases that came to the brain bank through sources where the focus of clinical research is on aging and dementia (Mayo Clinic Jacksonville Memory Disorder Clinic, State of Florida Alzheimer Disease Initiative; Einstein Aging Study; Florida Alzheimer's Disease Research Center) to determine if the atypical clinical diagnoses was influenced by referral source after excluding cases from sources not specializing in aging and dementia disorders.

Characteristic AD referral source	AD subtypes			Statistics	
	HpSp	Typical	LP	*p*	(stat test)
Number (% total of n=889)	81 (10%)	578 (75%)	116 (15%)		
Age, mean yr. (SD)	73 (9)	79 (10)	86 (6)	<0.001	(ANOVA)
Females (% total of AD type)	29 (36%)	323 (56%)	81 (70%)	<0.001	(chi-square)
Atypical clinical/Total (% total of AD type)	21/81 (28%)	67/578 (13%)	5/116 (5%)	<0.001	(chi-square)

Supplemental Table 5.

Three multiple logistic regressions were performed individually between the AD types to test whether *MAPT* remained significant in limbic predominant cases when controlling for presence Lewy body pathology (including brainstem (BLBD), transitional (TLBD) and diffuse (DLBD) types).

Multiple Logistic Equations: AD type (0 vs. 1) = LBD + MAPT

Dependent variable (AD type)	P value		Odds Ratio	
	LBD	MAPT	LBD	MAPT
Hippocampal sparing (0) vs. Typical AD (1)	0.013	0.064	3.35	1.75
Typical AD (0) vs. Limbic predominant (1)	0.78	0.083	0.92	1.60
Hippocampal sparing (0) vs. Limbic predominant (1)	0.043	0.003	3.06	2.99
Note: LBD – 0 = no BLBD, TLBD, or DLBD in postmortem diagnosis; MAPT – 0 = H2H2 or H1H2, 1 = H1H1				

Supplemental Table 6.

Validation cohort from Alzheimer Disease Patient Registry/Mayo Clinic Study on Aging

Characteristic	AD subtypes			Statistics	
	HpSp	Typical	LP	*p-value*	test
Number (% total of n=113)	9 (8%)	80 (69%)	24 (21%)		
Age, mean yr. (SD)	78 (9)	86 (7)	90 (5)	<0.001	ANOVA
Females (% total of AD type)	4 (44%)	48 (60%)	16 (67%)	0.509	chi-square
Education, mean yr. (SD)	15 (4)	14 (3)	13 (3)	0.515	ANOVA
Postmortem findings					
NFT Braak stage, median (IQR)	6 (5.0-6.0)	6 (5.0-6.0)	6 (5.0-6.0)	0.531	ANOVA on ranks
Neurofibrillary tangle counts					
CA1, median (IQR)	5 (3,7)	12 (3,17)	18 (13,29)	<0.001	ANOVA on ranks
Subiculum, median (IQR)	11 (8,15)	16 (10,29)	44 (34,54)	<0.001	ANOVA on ranks
Superior temporal, median (IQR)	16 (12,22)	8 (3,15)	4 (2,8)	<0.001	ANOVA on ranks
Inferior parietal, median (IQR)	11 (8,16)	6 (1,9)	2 (1,5)	<0.001	ANOVA on ranks
Mid-frontal, median (IQR)	14 (10,18)	4 (1,9)	2 (1,4)	<0.001	ANOVA on ranks
Clinical findings					
Age of onset, mean yr. (SD)	69 (9)	75 (8)	79 (7)	0.007	ANOVA
Disease duration, mean yr. (SD)	9 (2)	10 (4)	11 (5)	0.502	ANOVA
Atypical clinical/Total (% total of AD type)	3/9 (33%)	4/80 (5%)	0/24 (0%)	<0.001	chi-square
MMSE					
Initial score, median (IQR)*	25 (21,27)	26 (12,28)	25 (24,27)	0.880	ANOVA on ranks
Final score, median (IQR)*	12 (7,16)	14 (9,20)	13 (9,18)	0.703	ANOVA on ranks
Longitudinal decline, median (IQR)*	-2.8 (-4.3,-1.8)	-2.1 (-3.2,-1.0)	-1.4 (-2.1,-0.6)	0.040	ANOVA on ranks

Abbreviations: HpSp – hippocampal sparing (HS), Typical – classic progression of AD from limbic regions to cortex (T), LP – limbic predominant (LP), SD – standard deviation, IQR – interquartile range, ANOVA – analysis of variance; Total refers to the number of cases evaluated out of the group. *Median MMSE score assessed within 3 years of symptom onset (initial) or death (final).

Supplemental Table 7.

A series of AD cases that had were not included in the original algorithmic classification cohort were classified into subtypes by a neuropathologist using a Gestalt diagnosis and compared to subsequent algorithmic classification. Using the algorithmic classification as the "gold standard," the following sensitivity and specificity measures were calculated:

AD type	*Sensitivity*	*Specificity*
Hippocampal sparing	67%	93%
Typical AD	81%	61%
Limbic predominant	58%	92%