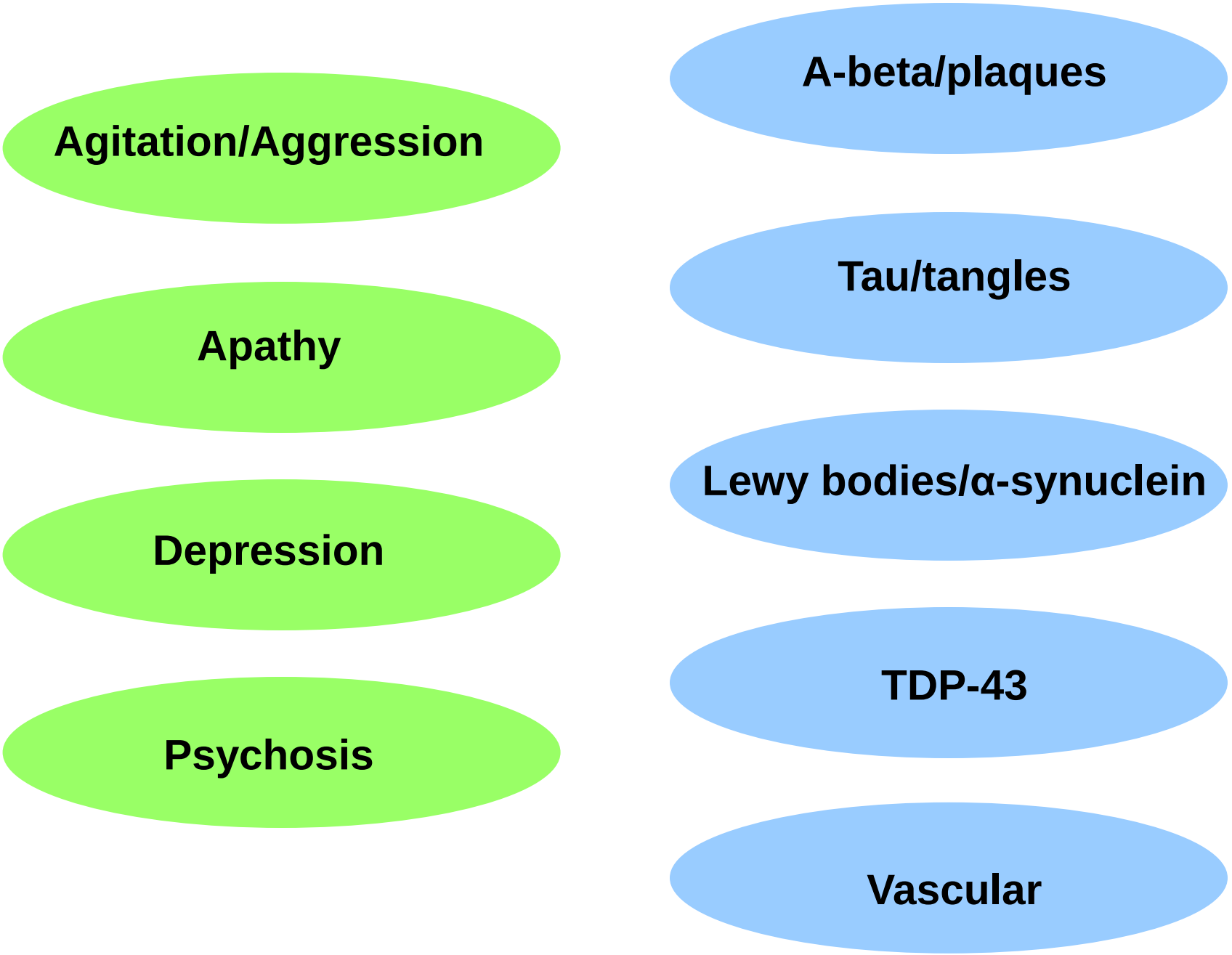
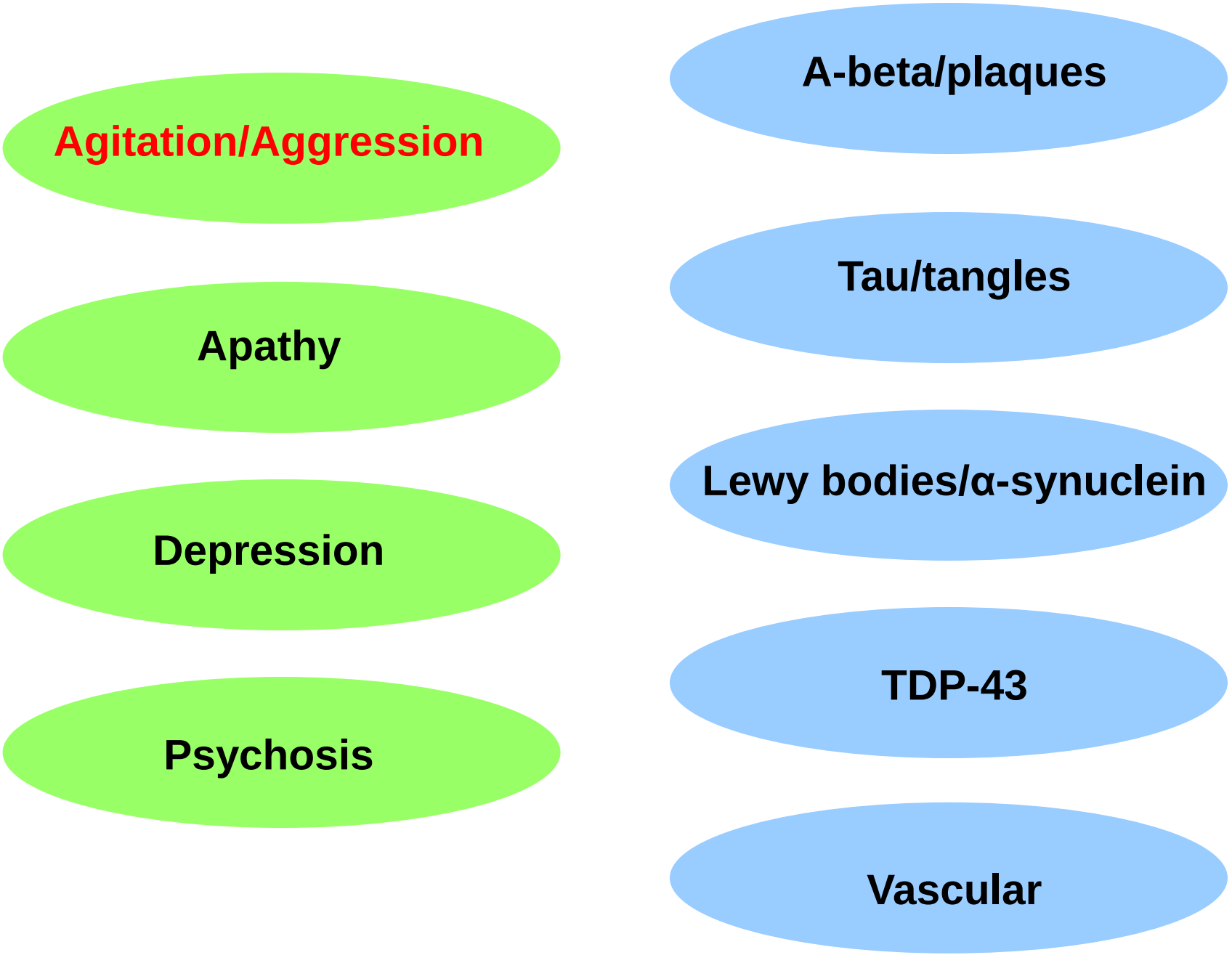
Neuropathologic correlates of BPSD

Julia Kofler, MD
University of Pittsburgh


Agitation/Aggression
Apathy
Depression
Psychosis
A-beta/plaques
Tau/tangles
Lewy bodies/α-synuclein
TDP-43
Vascular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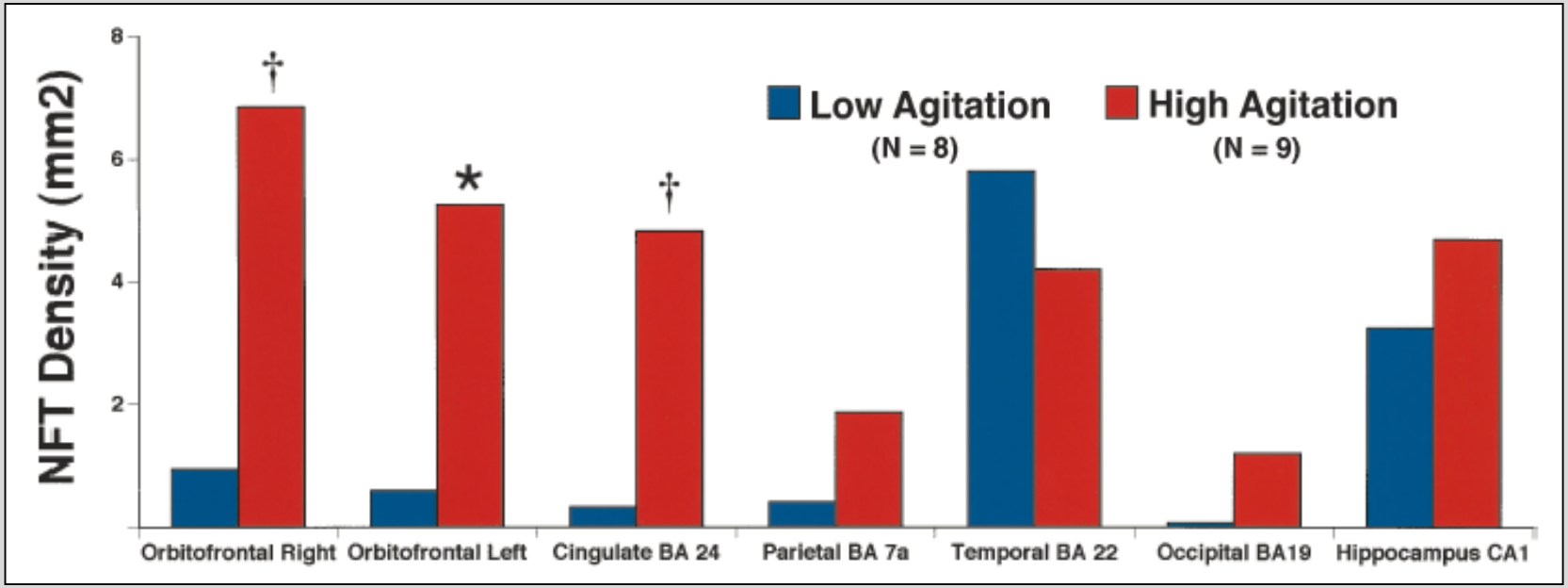
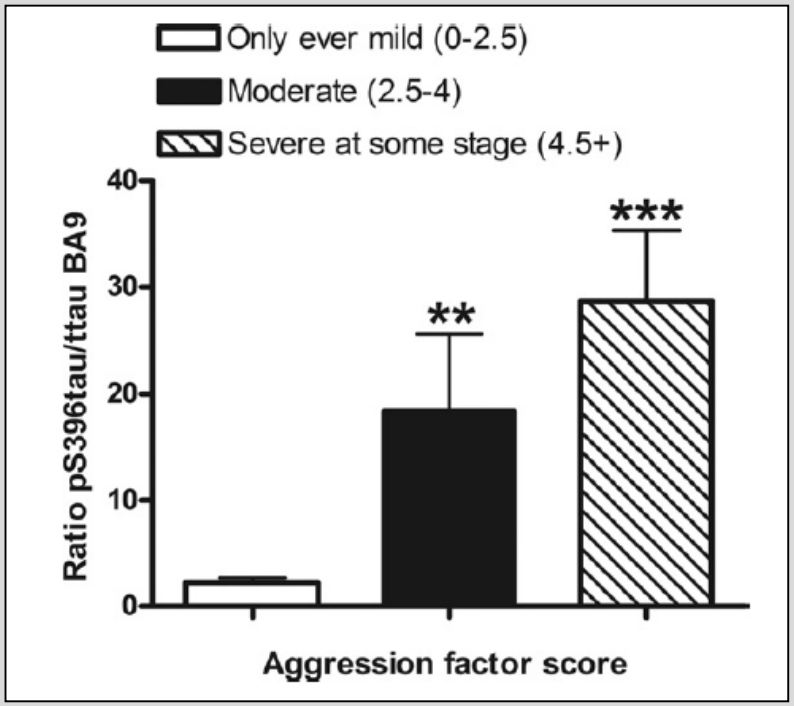


Tekin et al. Ann Neurol 2001



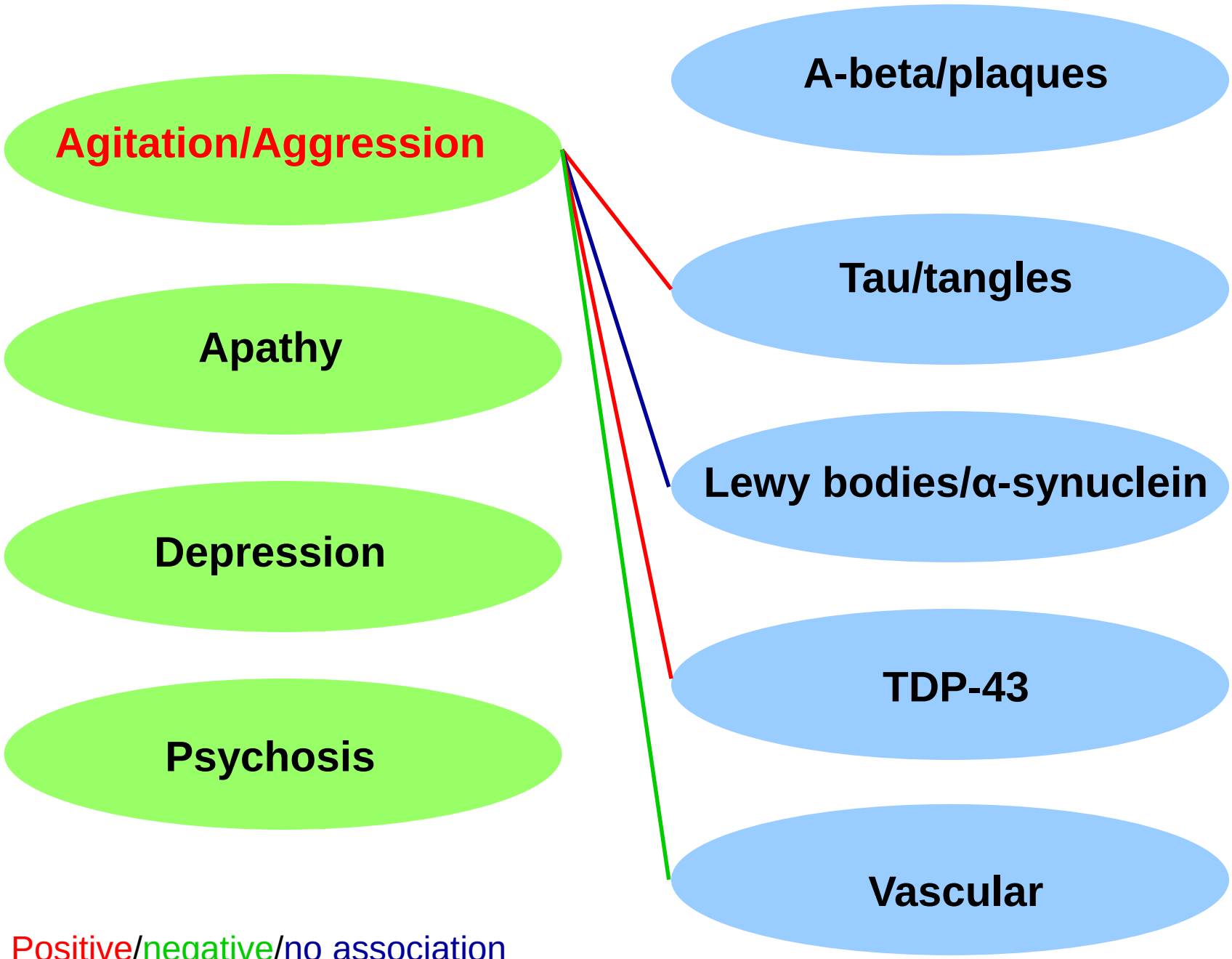
Guadagna et al. Neurobiol Aging 2012

Agitation/aggression: IAD 34.6%
HAD 49.6% (p=0.0001)

NACC variable	A(+)IAD	*A(−)IAD*	*p* value (<0.05)	NACC variable	A(+)HAD	*A(−)HAD*	*p* value (<0.05)
TAUOPATHY (N = 128)	N = 3/78, 3.85%	N = 5/136, 3.68%	0.950	**TAUOPATHY (N = 1114)**	N = 18/566, 3.18%	N = 30/548, 5.47%	0.059
CLINICAL LBDS (N = 192)	N = 14/75 18.24%	N = 19/117, 16.24%	0.183 *	**CLINICAL LBDS (N = 1406)**	N = 72/709, 10.16%	N = 45/697, 6.46%	0.012 *
Male (N = 118)	N = 9/52, 17.31%	N = 13/66, 19.70%	0.741 *	*Male (N = 765)*	N = 46/401, 11.47%	N = 29/364, 7.97%	0.104 *
Female (N = 74)	N = 9/23, 39.13%	N = 6/51, 11.76%	0.007 *	*Female (N = 641)*	N = 26/308, 8.44%	N = 16/333, 4.80%	0.063 *
ALPHA-SYNUCLEIN (N = 17)	N = 1/4, 25.00%	N = 4/13, 30.77%	0.825 *	**ALPHA-SYNUCLEIN (N = 250)**	N = 35/117, 29.91%	N = 39/133, 29.32%	0.919 *
CLINICAL FTD (N = 230)	N = 5/86, 5.81%	N = 6/144, 4.17%	0.571 *	**CLINICAL FTD (N = 1452)**	N = 43/724, 5.94%	N = 21/728, 2.88%	0.005 *
Male (N = 136)	N = 5/60, 8.33%	N = 4/76, 5.26%	0.475 *	*Male (N = 791)*	N = 30/411,7.30%	N = 14/380, 3.68%	0.027 *
Female (N = 94)	N = 0/26, 0.00%	N = 2/68, 2.94%	0.377 *	*Female (N = 661)*	N = 13/313,4.15%	N = 7/348, 2.01%	0.108 *
P-TDP-43(N = 12)	N = 2/3, 66.67%	N = 4/9, 44.44%	0.505 *	**P-TDP-43(N = 231)**	N = 45/107, 42.06%	N = 30/124, 24.19%	0.004 *
Male (N = 7)	N=l/1, 100%	N = 2/6, 33.33%	0.212 *	*Male (N = 123)*	N = 24/57, 42.11%	N = 15/66, 22.73%	0.021 *
Female (N = 5)	N =l/2, 50%	N = 2/3, 66.66%	0.709 *	*Female (N = 108)*	N = 29/50, 58%	N = 43/58, 74.14%	0.076 *

NACC variable	A(+)IAD	*A(−)IAD*	*p* value (<0.05)	NACC variable	A(+)HAD	*A(−)HAD*	*p* value (<0.05)
LACUNES & INFARCTS (N = 256)	N = 16/89, 17.98%	N = 50/167, 29.94%	0.037 *	**LACUNES & INFARCTS (N = 1454)**	N = 134/723, 18.53%	N = 132/731 18.06%	0.814 *
Male (N = 149)	N = 12/62, 19.35%	N = 26/87, 29.88%	0.146 *	*Male (N = 792)*	N = 77/411, 18.73%	N = 78/381, 20.47%	0.538 *
Female (N = 107)	N = 4/27, 14.81%	N = 24/80, 30.00%	0.121 *	*Female (N = 662)*	N = 57/312, 18.27%	N = 54/350, 15.43%	0.329 *
LARGE ARTERIAL INFARCTS (N = 230)	N = 5/82, 6.10%	N = 23/148, 15.54%	0.036 *	**LARGE ARTERIAL INFARCTS (N = 1146)**	N = 39/579, 6.77%	N = 39/567, 6.88%	0.924 *
Male (N = 133)	N = 4/58, 6.90%	N = 12/75, 16%	0.110 *	*Male (N = 635)*	N = 19/339, 5.60%	N = 23/296, 7.77%	0.273 *
Female (N = 97)	N = 1/24, 4.17%	N = 11/73, 15.07%	0.159 *	*Female (N = 511)*	N = 20/240, 8.33%	N = 16/271, 5.90%	0.284 *
SEV of ATHER in C of W (N = 254)	N = 32/88, 36.36%	N = 70/166, 42.17%	0.369 **	**SEV of ATHER in C of W (N = 1444)**	N = 276/718, 38.44%	N = 318/726, 43.80%	0.038 **
Male (N = 148)	N = 20/61, 32.79%	N = 38/87, 43.68%	0.182 **	*Male (N = 785)*	N = 154/407, 37.84%	N = 164/378, 43.39%	0.114 **
Female (N = 106)	N = 12/27, 44.44%	N = 32/79, 40.51%	0.720 **	*Female (N = 659)*	N = 122/311, 39.23%	N = 154/348, 44.25%	0.192 **

Sennik et al,J Alzheimers Dis 2017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Positive/negative/no association

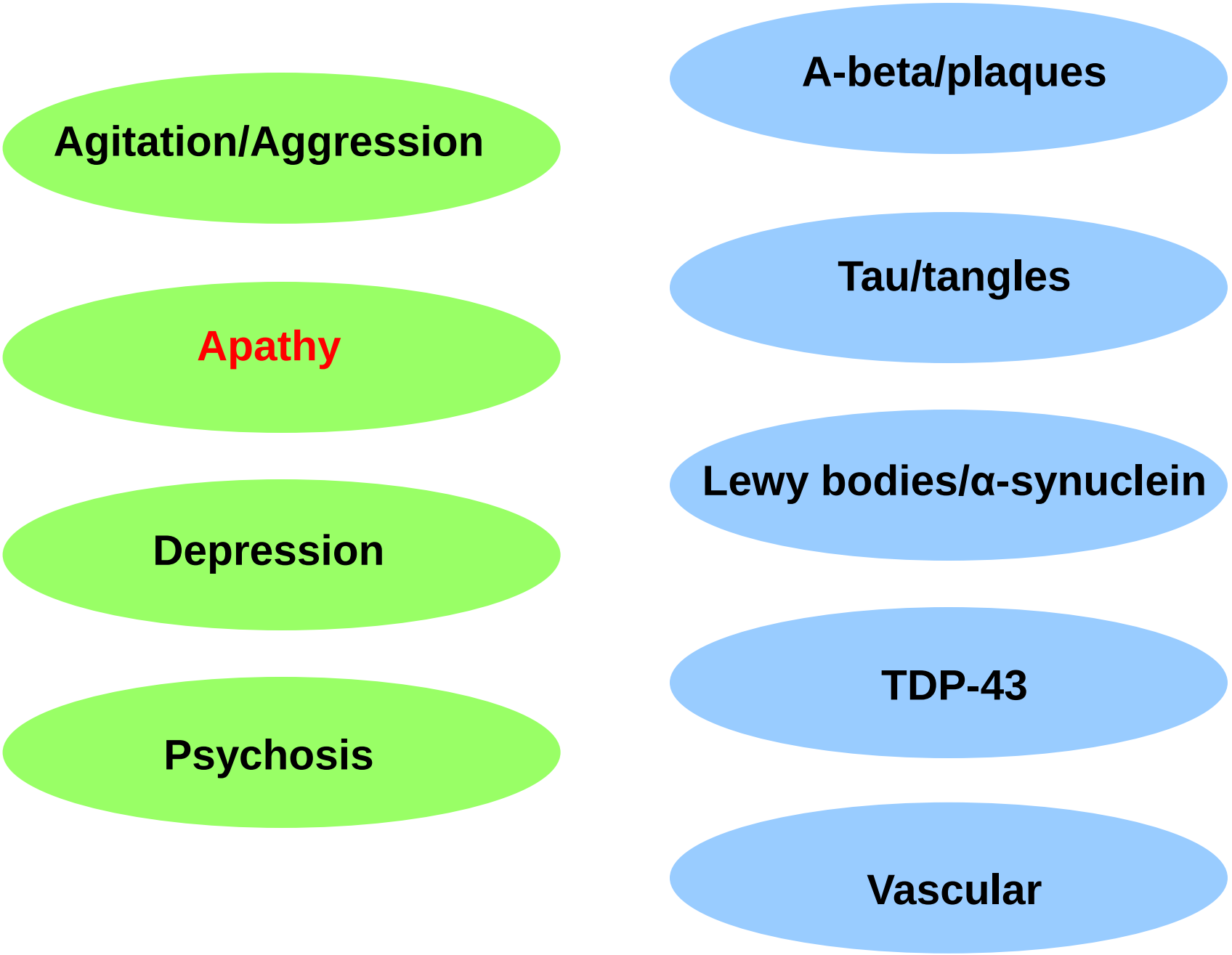
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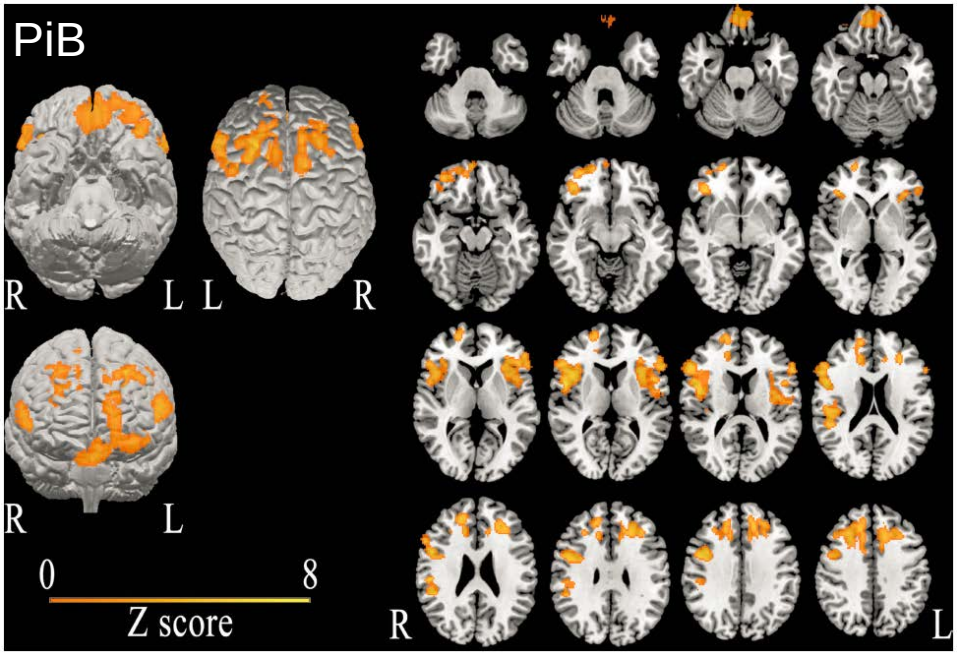
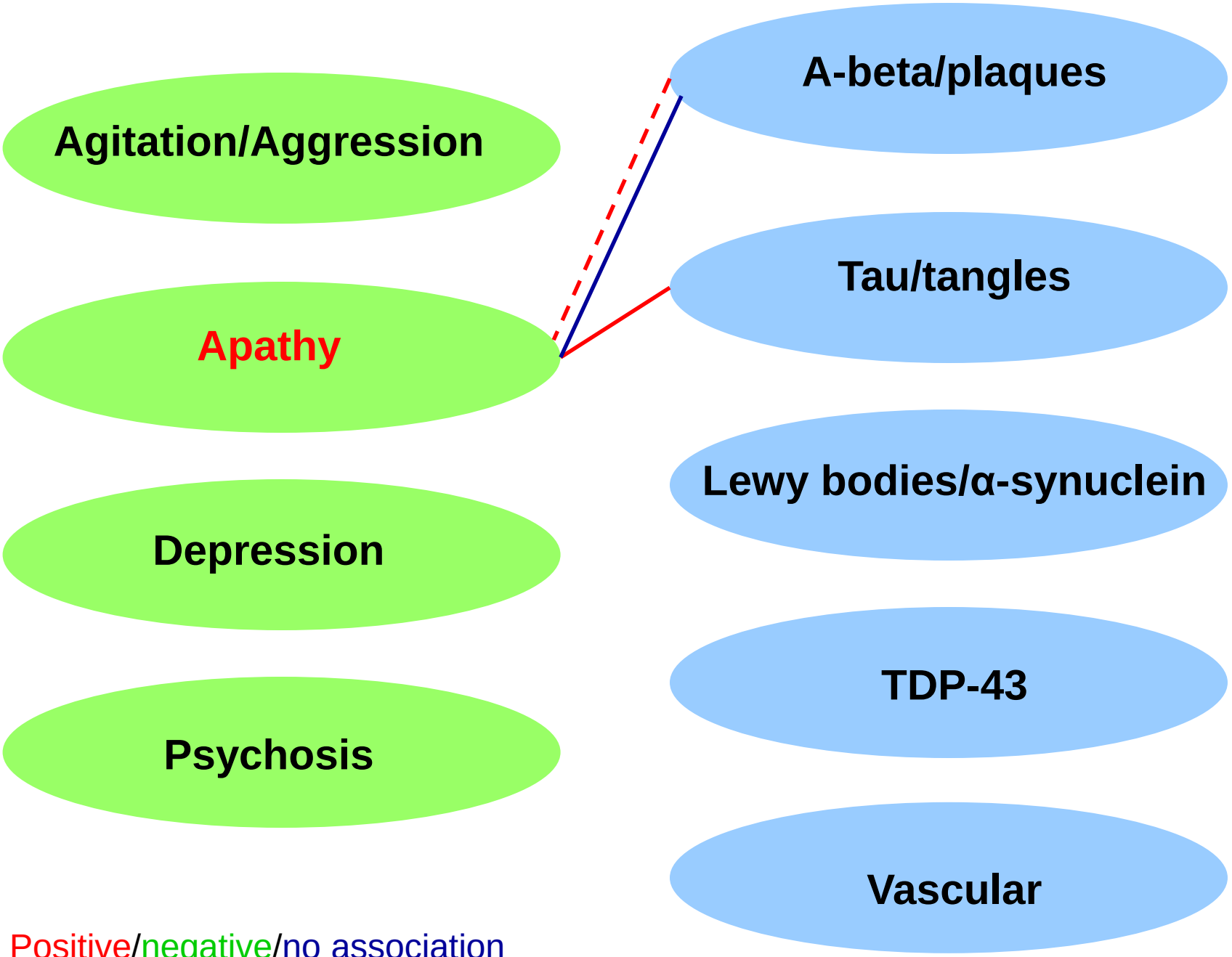
Table 1. Pearson correlation coefficients between mean and regional NFT and NP counts and chronic apathy and total NPI scores

Brain region	n	Chronic apathy				Chronic total NPI			
		NFT		NP		NFT		NP	
1st hypothesized region									
Anterior cingulate	24	r = 0.518	p = 0.01	r = –0.098	p = 0.65	r = 0.438	p = 0.032	r = –0.011	p = 0.96
2nd hypothesized regions									
Left orbital frontal	27	r = 0.218	p = 0.27	r = –0.005	p = 0.98	r = 0.191	p = 0.34	r = –0.179	p = 0.37
Right orbital frontal	24	r = 0.233	p = 0.27	r = 0.129	p = 0.55	r = 0.200	p = 0.35	r = 0.046	p = 0.83
3rd hypothesized regions									
Lateral parietal	24	r = 0.326	p = 0.12	r = 0.137	p = 0.52	r = 0.098	p = 0.65	r = –0.110	p = 0.61
Superior temporal	28	r = 0.216	p = 0.27	r = –0.012	p = 0.95	r = 0.239	p = 0.22	r = –0.028	p = 0.89
Control regions									
Occipital	26	r = 0.354	p = 0.076	r = 0.308	p = 0.13	r = 0.273	p = 0.18	r = 0.314	p = 0.12
CA1	28	r = 0.076	p = 0.70	r = 0.127	p = 0.52	r = 0.229	p = 0.24	r = 0.167	p = 0.40
Prosubiculum	28	r = 0.207	p = 0.29	r = 0.017	p = 0.93	r = 0.356	p = 0.063	r = 0.228	p = 0.24
Mean of all regions	29	r = 0.352	p = 0.061	r = 0.125	p = 0.52	r = 0.318	p = 0.093	r = 0.048	p = 0.80



Marshall et al.
Dement Geriatr Cogn Disord 2006

Mori et al.
J Neurol Neurosurg Psychiatry 2014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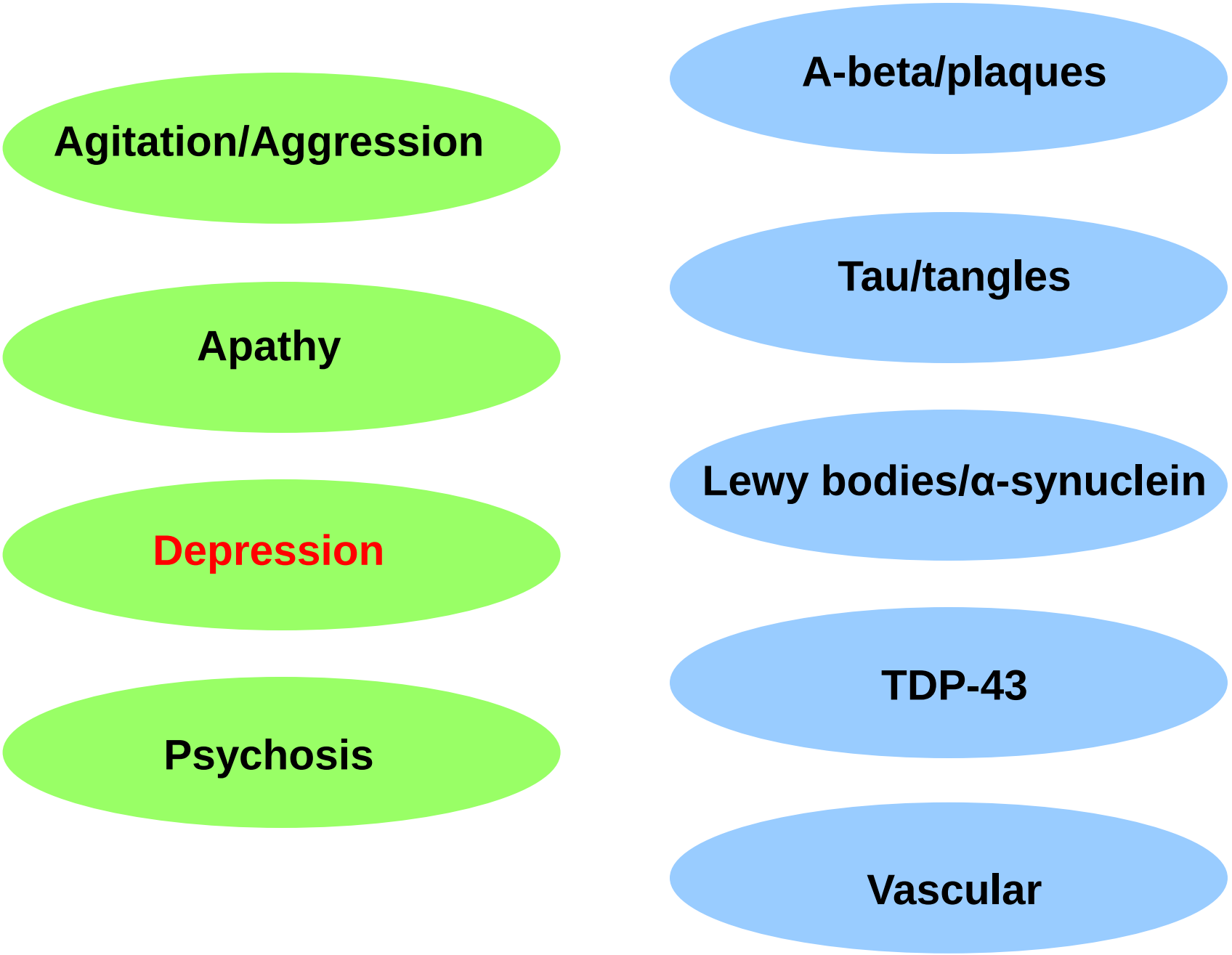
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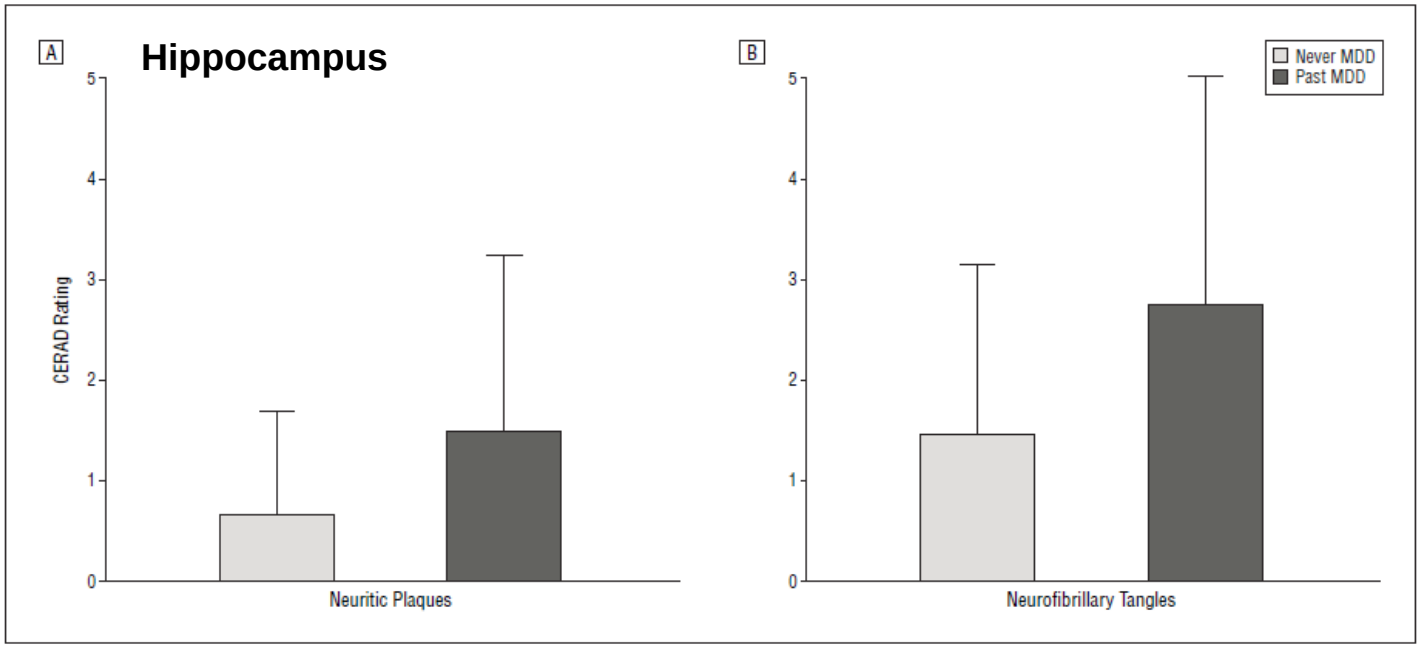
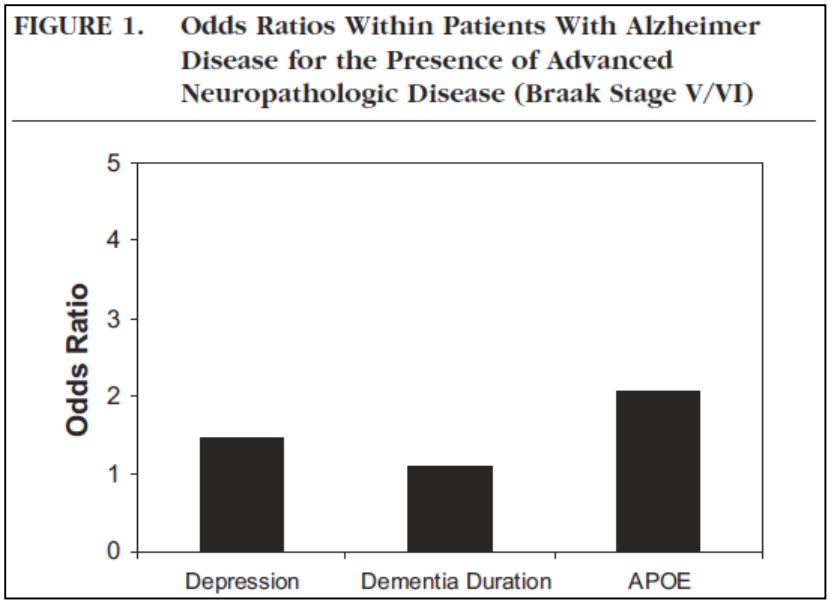


Rapp et al. Arch Gen Psychiatry 2006



Rapp et al. Am J Geriatr Psychiatry 2008

No association with CERAD plaque scores

Lewy bodies in the amygdala increase risk for major depression in subjects with Alzheimer disease

O.L. Lopez, MD; J.T. Becker, PhD; R.A. Sweet, MD; F.J. Martin-Sanchez, MD; and R.L. Hamilton, MD

NEUROLOGY 2006;67:660–665

	No depression (%)	Depression (%)	χ^2	*p* Value
All cases*				
AD alone	114 (91)	11 (9)	4.41	0.01
All AD + LB	117 (82)	25 (18)		
LB regions†				
Amygdala only	18 (69)	8 (31)	9.44	0.002
Score 1–2‡	20 (95)	1 (5)	0.38	0.53
Score 3–6‡	23 (88.5)	3 (11.5)	0.19	0.66
Score 7–10‡	56 (81)	13 (14)	4.13	0.04

Int J Geriatr Psychiatry. 2016 December ; 31(12): 1301–1311. doi:10.1002/gps.4435.

Clinicopathological correlates of depression in early Alzheimer's disease in the NACC

Sarah T. McCutcheon[1], Dingfen Han[2], Juan Troncoso[3], Vassilis E. Koliatsos[2,3,4], Marilyn Albert[4], Constantine G. Lyketsos[2], and Jeannie-Marie S. Leoutsakos[2]

No association with Braak stage or NP scores

Cortical Amyloid β Deposition and Current Depressive Symptoms in Alzheimer Disease and Mild Cognitive Impairment

Journal of Geriatric Psychiatry and Neurology
2016, Vol. 29(3) 149-159

DOI: 10.1177/0891988715606230
jgpn.sagepub.com
SAGE

Jun Ku Chung, HBSc[1,2], Eric Plitman, BSc[1,2], Shinichiro Nakajima, MD, PhD[2,3,4,5], M. Mallar Chakravarty, PhD[6,7], Fernando Caravaggio, HBSc[1,2], Philip Gerretsen, MD, PhD[2,3,5], Yusuke Iwata, MD[2,4], and Ariel Graff-Guerrero, MD, PhD[1,2,3,5]; for the Alzheimer's Disease Neuroimaging Initiative

No association with PET amyloid burden

Robert S. Wilson, PhD
Ana W. Capuano, PhD
Patricia A. Boyle, PhD
George M. Hoganson, MD
Loren P. Hizel, BA
Raj C. Shah, MD
Sukriti Nag, MD
Julie A. Schneider, MD
Steven E. Arnold, MD
David A. Bennett, MD

Clinical-pathologic study of depressive symptoms and cognitive decline in old age

Neurology® 2014;83:702-709

- **Amyloid and tangle burden, neocortical Lewy bodies, hippocampal sclerosis, gross infarcts or microinfarcts were not related to depressive symptoms or change in symptoms over time**
- **Depressive symptoms have an association with cognitive decline that is independent of the neuropathologic hallmarks of dementia**

Alzheimer's disease pathology does not mediate the association between depressive symptoms and subsequent cognitive decline

Donald R. Royall[a,b,c,d,*], Raymond F. Palmer[c]

Alzheimer's & Dementia 9 (2013) 318–325

- **No association with plaque and tangle counts, cortical Lewy bodies or gross, lacunar and microinfarcts**

Correlates of depression in cognitively normal subjects

Table 2 Associations between neuropathology associated with Alzheimer's disease and previous depression

	n	*n* (%) with depression	*P*
Maximum score across neocortex			
Neuritic plaques			0.42
None	68	18 (26)	
Mild	42	11 (26)	
Moderate or greater	43	7 (16)	
Diffuse plaques			0.10
None	48	12 (25)	
Mild	33	12 (36)	
Moderate or greater	71	12 (17)	
Tangles			0.27
None	92	18 (20)	
Mild	52	16 (31)	
Moderate or greater	7	1 (14)	
Maximum score in entorhinal cortex and hippocampus			
Neuritic plaques			0.78
None	69	17 (25)	
Mild	45	9 (20)	
Moderate or greater	39	10 (26)	
Diffuse plaques			0.92
None	62	16 (24)	
Mild	42	10 (22)	
Moderate or greater	46	10 (22)	
Tangles			0.75
None	19	3 (16)	
Mild	40	9 (23)	
Moderate or greater	93	23 (25)	
Nucleus basalis			
Tangles			0.23
None	42	6 (14)	
Mild	37	11 (30)	
Moderate or greater	22	6 (27)	
Plaques			0.44
None	79	18 (23)	
Mild	7	3 (43)	
Moderate or greater	3	0	
Substantia nigra			
Tangles			0.28
None	115	27 (23)	
Mild	30	7 (23)	
Moderate or greater	3	2 (67)	
Lewy bodies			0.025
None	142	32 (23)	
Mild	5	1 (20)	
Moderate or greater	3	3 (100)	
Locus ceruleus			
Tangles			0.051
None	69	17 (25)	
Mild	38	8 (21)	
Moderate or greater	10	6 (60)	
Lewy bodies			0.035
None	114	28 (25)	
Mild	3	1 (33)	
Moderate or greater	3	3 (100)	
Raphe nucleus			
Tangles			0.76
None	75	18 (24)	
Mild	20	3 (15)	
Moderate or greater	21	5 (24)	

Tsopelas et al. Br J Psychiatry 2011

No Association of Lower Hippocampal Volume With Alzheimer's Disease Pathology in Late-Life Depression

François-Laurent De Winter, M.D., Louise Emsell, Ph.D., Filip Bouckaert, M.D., Lene Claes, M.Sc., Saurabh Jain, M.Sc., Gill Farrar, Ph.D., Thibo Billiet, Ph.D., Stephan Evers, M.Sc., Jan Van den Stock, Ph.D., Pascal Sienaert, M.D., Ph.D., Jasmien Obbels, M.Sc., Stefan Sunaert, M.D., Ph.D., Katarzyna Adamczuk, Ph.D., Rik Vandenberghe, M.D., Ph.D., Koen Van Laere, M.D., Ph.D., Mathieu Vandenbulcke, M.D., Ph.D.

Am J Psychiatry 2017; 174:237–245,

- **No association with cortical amyloid burden by PET**

Amyloid burden and incident depressive symptoms in preclinical Alzheimer's disease

Stephanie Perin[a,c,*], Karra D. Harrington[b], Yen Ying Lim[b], Kathryn Ellis[b,c], David Ames[c,d], Robert H. Pietrzak[e,f], Adrian Schembri[g], Stephanie Rainey-Smith[h,i], Olivier Salvado[j], Simon M. Laws[h,k,1], Ralph N. Martins[h,i], Victor L. Villemagne[b,l,m], Christopher C. Rowe[l,m], Colin L. Masters[b], Paul Maruff[b,g], for the AIBL research group

Journal of Affective Disorders 229 (2018) 269–274

- **No association with positivity on amyloid PET**

Depressive symptoms and tau accumulation in the inferior temporal lobe and entorhinal cortex in cognitively normal older adults: a pilot study

Jennifer R. Gatchel, M.D., Ph.D.[a,b], **Nancy J. Donovan, M.D.**[a,c,d,e], **Joseph J. Locascio, Ph.D.**[f], **Aaron P. Schultz, Ph.D.**[f], **J. Alex Becker, Ph.D.**[g], **Jasmeer Chhatwal, M.D., Ph.D.**[f], **Kathryn V. Papp, Ph.D.**[c,e], **Rebecca E. Amariglio, Ph.D.**[c,e], **Dorene M. Rentz, Psy.D.**[c,e,f], **Deborah Blacker, M.D., Sc.D.**[a,h], **Reisa A. Sperling, M.D.**[c,e,f], **Keith A. Johnson, M.D.**[c,e,f,g], and **Gad A. Marshall, M.D.**[c,e,f]

J Alzheimers Dis. 2017 ; 59(3): 975–985.

- **Depressive symptoms are modestly associated with increased with tau burden in inferior temporal and entorhinal cortex by PET**
- **No association with amyloid burden by PET**

Longitudinal Association of Amyloid Beta and Anxious-Depressive Symptoms in Cognitively Normal Older Adults

Nancy J. Donovan, M.D., Joseph J. Locascio, Ph.D., Gad A. Marshall, M.D., Jennifer Gatchel, M.D., Ph.D., Bernard J. Hanseeuw, M.D., Ph.D., Dorene M. Rentz, Psy.D., Keith A. Johnson, M.D., Reisa A. Sperling, M.D., for the Harvard Aging Brain Study

AJP in Advance (doi: 10.1176/appi.ajp.2017.17040442)

- **Higher amyloid burden was associated with increasing anxious-depressive symptoms over time**

Aizenstein et al. BMC Medicine (2016) 14:161
DOI 10.1186/s12916-016-0720-5

BMC Medicine

Vascular Dementia

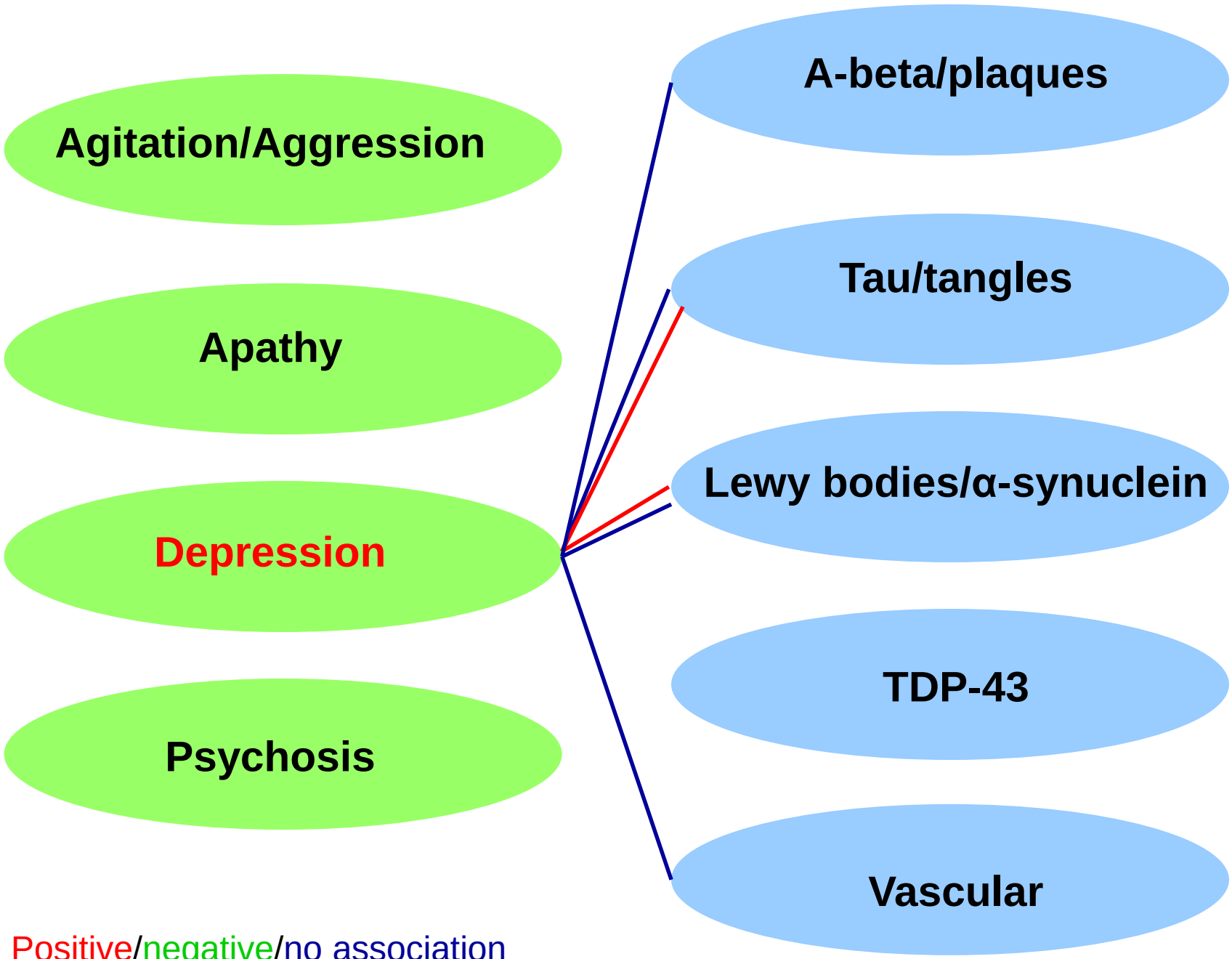
OPINION Open Access

Vascular depression consensus report – a critical update

Howard J. Aizenstein[1], Andrius Baskys[2], Maura Boldrini[3,4], Meryl A. Butters[5], Breno S. Diniz[6], Manoj Kumar Jaiswal[3,7], Kurt A. Jellinger[8*], Lev S. Kruglov[9], Ivan A. Meshandin[10], Milija D. Mijajlovic[11], Guenter Niklewski[12], Sarah Pospos[2], Keerthy Raju[13], Kneginja Richter[12,14], David C. Steffens[15], Warren D. Taylor[16,17] and Oren Tene[18,19]

Table 2 Negative neuropathology findings in late-life depression

Findings	Reference
No association with microvascular disease	[179]
Cerebrovascular pathology (hemorrhages, infarcts, microinfarcts, lacunes) not more severe than in non-depressed aged	[31, 175, 176, 180]
No increased white matter change	[31, 176]
No increased Alzheimer's disease pathology	[31, 176, 180, 181]
No increased cerebral amyloid angiopathy (but association between plaque and tangle pathology and life time depression preceding Alzheimer's disease diagnosis)	[182, 183]
No hippocampal sclerosis	[31]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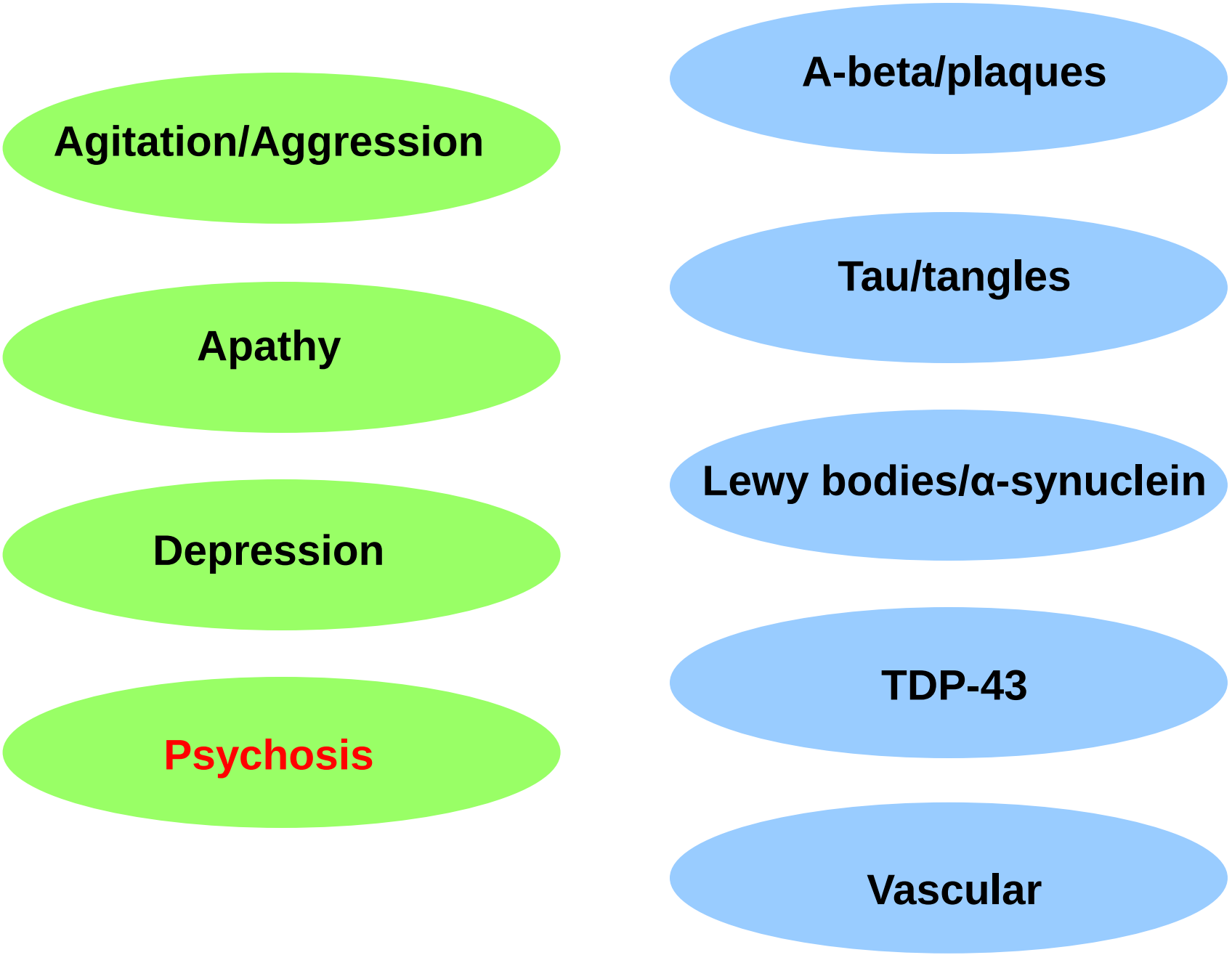
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Psychosis in AD

- Defined as occurrence of delusions or hallucinations
- 40-60% of AD patients
- Most rapid rate increase in early to middle AD stages
- Psychosis is associated with
  - Worse cognitive impairment and more rapid cognitive decline
  - Higher rate of institutionalization and caregiver stress
  - Higher mortality
  - Higher rates of additional neuropsychiatric disturbances, e.g. aggression, agitation, depression

Psychosis in AD

- **Psychosis aggregates in families**
  - **Heritability is 30-60%**
- **In imaging studies, psychosis is associated with**
  - **Reduced cortical gray matter volume**
  - **Reduced cortical blood flow**
  - **Reduced cortical glucose metabolism**

Table 3.—Densities of Neurofibrillary Tangles in 27 AD Patients With or Without Psychosis*

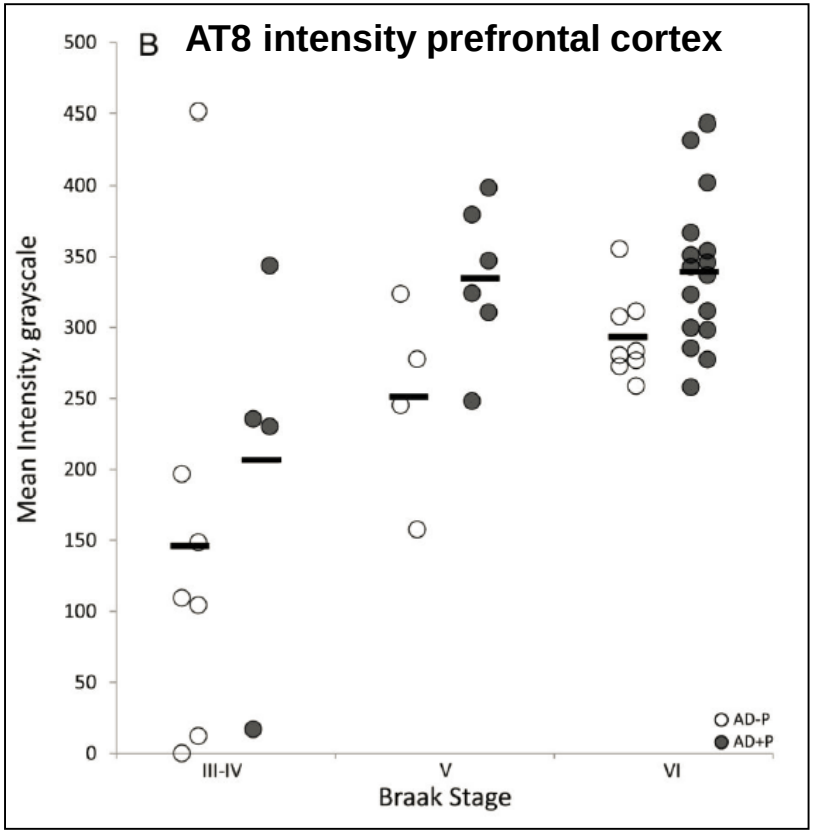
	Psychosis		
	Absent	Present	P
Neocortex			
Middle frontal cortex	4.6 ± 4.5	11.0 ± 8.9	.04†
Superior temporal cortex	9.9 ± 8.4	12.8 ± 10.5	.68
Allocortex			
Prosubiculum	20.5 ± 14.6	21.2 ± 10.0	.81
Entorhinal cortex	10.8 ± 6.9	13.0 ± 5.0	.53

Zubenko et al.
Arch Neurol 1991

Table 4. Neurofibrillary Tangle Densities in Individuals With vs Without Psychosis by Brain Region

	Density ± SD,* No./mm²		ANOVA†	
Brain Region	With Psychosis	Without Psychosis	F Score	P
Middle frontal gyrus	7.9 ± 9.7	2.8 ± 5.5	$F_{1,107} = 6.98$	.01
Superior temporal cortex	11.9 ± 15.2	5.2 ± 7.9	$F_{1,107} = 7.28$	.008
Inferior parietal lobule	7.4 ± 10.0	4.0 ± 7.4	$F_{1,106} = 7.91$	.006
Hippocampus	36.0 ± 32.6	27.6 ± 28.7	$F_{1,106} = 0.51$	.5
Entorhinal cortex	19.3 ± 18.0	14.1 ± 10.1	$F_{1,106} = 1.11$	.3

Farber et al. Arch Gen Psychiatry 2000



Murray et al. J Alzheimers Dis 2014

Table 2.—Densities of Senile Plaques in 27 AD Patients With or Without Psychosis*

	Psychosis		
	Absent	Present	P
Neocortex			
Middle frontal cortex	20.2 ± 15.4	25.5 ± 9.7	.26
Superior temporal cortex	16.3 ± 10.4	20.9 ± 6.3	.13
Allocortex			
Prosubiculum	5.6 ± 4.3	11.1 ± 5.6	.007†
Entorhinal cortex	11.0 ± 7.3	11.8 ± 4.3	.33

Zubenko et al.
Arch Neurol 1991

Table 5. Total and Cored SP Densities in Individuals With vs Without Psychosis*

	Statistical Result	
Statistical Comparison	F Score	P
Total SPs		
Psychosis × CDR × region	$F_{12,392} = 0.65$	.8
Psychosis × region	$F_{4,392} = 0.58$	.7
CDR × region	$F_{12,392} = 1.24$	.2
Psychosis × CDR	$F_{3,98} = 0.06$	.9
Region	$F_{4,392} = 69.3$	<.001
CDR	$F_{3,98} = 4.09$	.009
Psychosis	$F_{1,98} = 0.02$	.9
Cored SPs		
Psychosis × CDR × region	$F_{12,396} = 0.52$	.9
Psychosis × region	$F_{4,396} = 0.47$	.8
CDR × region	$F_{12,396} = 1.49$	.1
Psychosis × CDR	$F_{3,99} = 0.13$	.9
Region	$F_{4,396} = 36.1$	<.001
CDR	$F_{3,99} = 5.66$	.001
Psychosis	$F_{1,99} = 0.63$	.4

Farber et al. Arch Gen Psychiatry 2000

	Any Psychosis	
	Absent (n = 25)	Present (n = 24)
Neuritic plaques		
Middle frontal cortex	24 (96)	22 (92)
Hippocampus	20 (80)	22 (92)
Inferior parietal cortex	23 (92)	23 (96)
Superior temporal cortex	23 (92)	24 (100)*
Occipital cortex	22 (88)	22 (92)
Transentorhinal cortex	24 (96)	23 (96)

Sweet et al.Int Psychogeriatr 2000

Results of statistical analysis comparing neuropathologically diagnosed AD patients (npAD) with and without psychosis. The gray cells represent non-significant associations

Variable	Psychosis status			
	npAD+P	npAD+D	npAD+H	npAD+DH
Lewy Bodies	OR = 1.825, 95% CI, –0.927 to –0.278, Wald $\chi^2(1)$ = 13.255, $p < 0.001$	OR = 0.690, 95% CI, –0.33 to.775, Wald $\chi^2(1)$ = 3.235, $p = 0.073$	OR = 0.444, 95% CI, 0.223 to 1.399, Wald $\chi^2(1)$ = 7.309, $p = 0.01$	OR = 0.408, 95% CI, 0.385 to 1.408, Wald $\chi^2(1)$ = 11.808, $p = 0.001$
Subcortical Arteriosclerotic Leukoen-cephalopathy	$\chi^2(1, N = 724)$ = 9.377, $p = 0.002$			$\chi^2(1, N = 533)$ = 9.882, $p = 0.002$

No association with Braak stage or CERAD plaque scores

Fischer et al. J Alzheimers Dis 2016

	Total (n = 145)	AD with Psychosis (n = 50)	AD without Psychosis (n = 95)	p-value
VASC, (Yes), n (%)	121 (83.4)	44 (88.0)	77 (81.1)	0.404**
LINF, (Yes), n (%)	9 (6.2)	4 (8.0)	5 (5.3)	0.496**
MICRO, (Yes), n (%)	19 (13.1)	11 (22.0)	8 (8.4)	0.041**
LAC, (Yes), n (%)	21 (14.5)	7 (14.0)	14 (14.7)	1.000**
HEM (Yes), n (%)	13 (9)	5 (10.0)	8 (8.4)	0.763**
ART (Yes), n (%)	32 (22.1)	12 (24.0)	20 (21.1)	0.845**
NEC (Yes), n (%)	1 (0.7)	0 (0.0)	1 (1.0)	1.000**
SCL (Yes), n (%)	15 (10.3)	4 (8.0)	11 (11.6)	0.727**
AVAS (Moderate and Severe), n (%)	57 (39.3)	21 (42.0)	36 (37.9)	0.762**
ARTER (Moderate and Severe), n (%)	55 (37.9)	28 (56.0)	27 (28.4)	0.002**
AMY (Moderate and Severe), n (%)	66 (45.5)	18 (36.0)	48 (50.5)	0.135**

Ting et al. Sci Rep 2016

Patient cohort

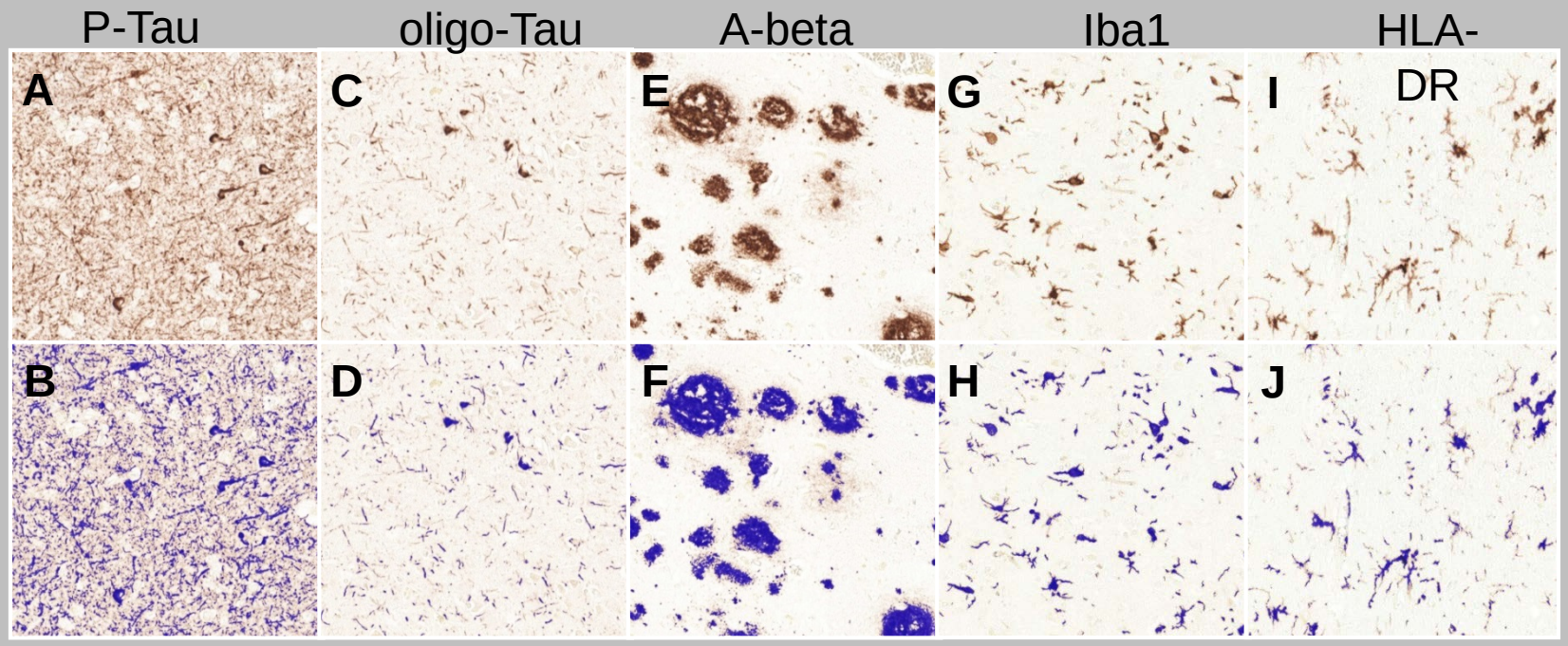
- 140 cases from University of Pittsburgh ADRC neuropathology core (1993-2014)
- Primary pathology diagnosis of AD
  - Intermediate to high (NIA-RI)
  - Braak stage III-V
  - End-stage cases (Braak VI) excluded
- Psychosis was defined as the presence of delusions or hallucinations at any visit
  - CERAD behavioral rating scale

	AD - P (n = 59 [42%])	AD + P (n = 81 [58%])	p
Age at death (yrs)	83.3 ± 7.8	82.1 ± 6.5	0.35
Gender Male Female	 32 (54%) 27 (46%)	 44 (54%) 37 (46%)	1.0
PMI (hours)	6.6 ± 5	6.5 ± 5	0.87
Age of onset (yrs)	74.6 ± 8.1	72.7 ± 6.7	0.36
Duration of illness (yrs)	7.6 ± 3.2	8.6 ± 3.6	0.09
Braak stage III IV V	 9 (15%) 28 (47%) 22 (37%)	 12 (15%) 26 (32%) 43 (53%)	0.14
ApoE ε4 positive (%)	29 (52%)	45 (56%)	0.73

Neuropathological disease burden in dorsolateral prefrontal cortex

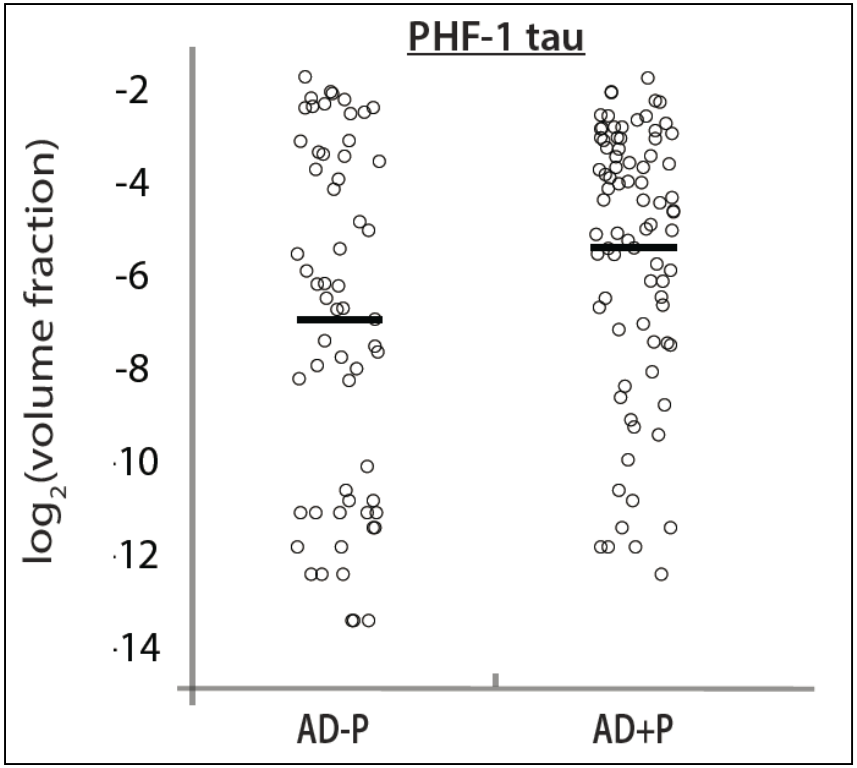
P-Tau

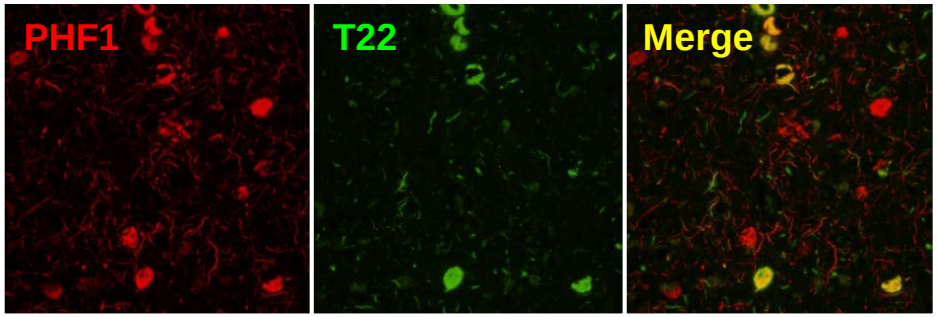
Iba1

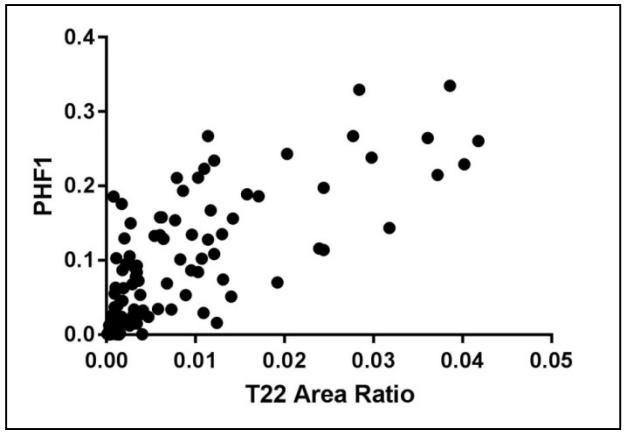


Univariate analysis

Variable		AD-P (N=59)	AD+P (N=81)	P
PHF-1 tau	Volume fraction Log_2(volume fraction)	0.009 [0.0001, 0.3347] -6.86 (3.76)	0.025 [0.0002, 0.3294] -5.30 (2.84)	0.01
Oligomeric tau	Volume fraction Log_2(volume fraction)	0.002 [0.0001, 0.0418] -9.22 (2.37)	0.003 [0.0002, 0.0402] -8.57 (2.08)	0.10
Aβ	Volume fraction Log_2(volume fraction)	0.037 [0.0008, 0.1098] -4.76 (1.34)	0.037 [0.0018, 0.1298] -4.76 (1.15)	0.99



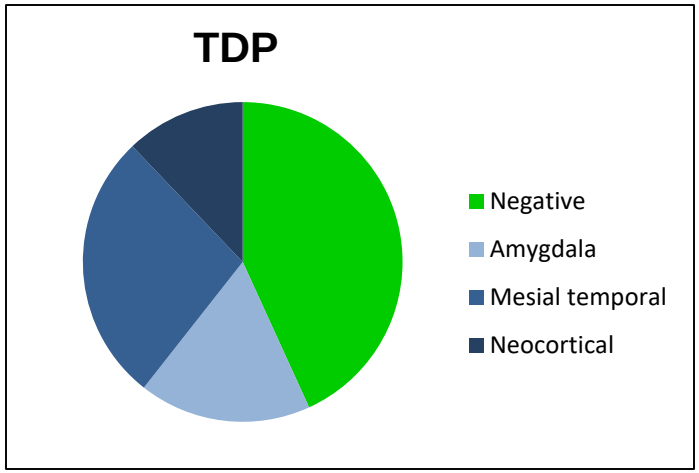


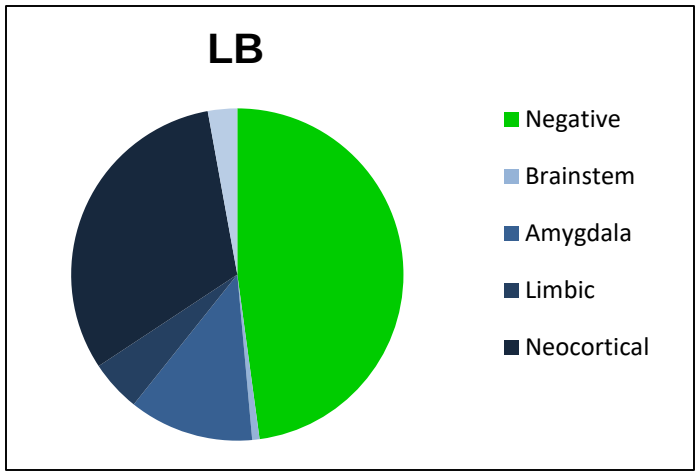


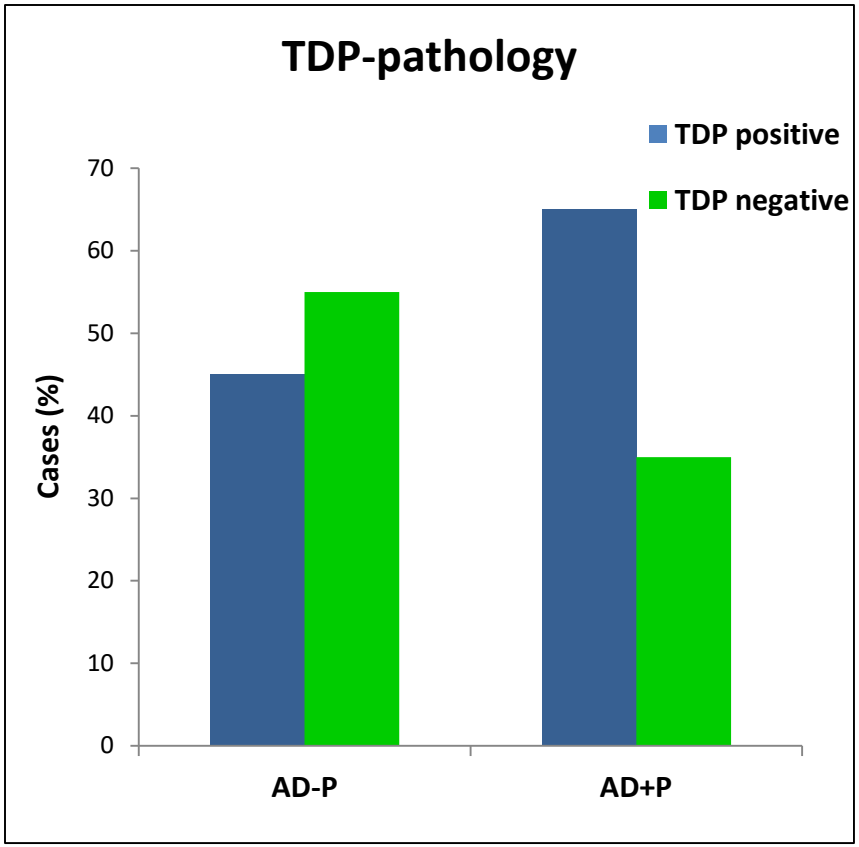
P < 0.0001
Spearman
r=0.84

Univariate analysis

Variable		AD-P (N=59)	AD+P (N=81)	P
Lewy pathology	Positive Negative	43% 57%	56% 44%	0.20
TDP-43 pathology	Positive Negative	45% 55%	65% 35%	0.04

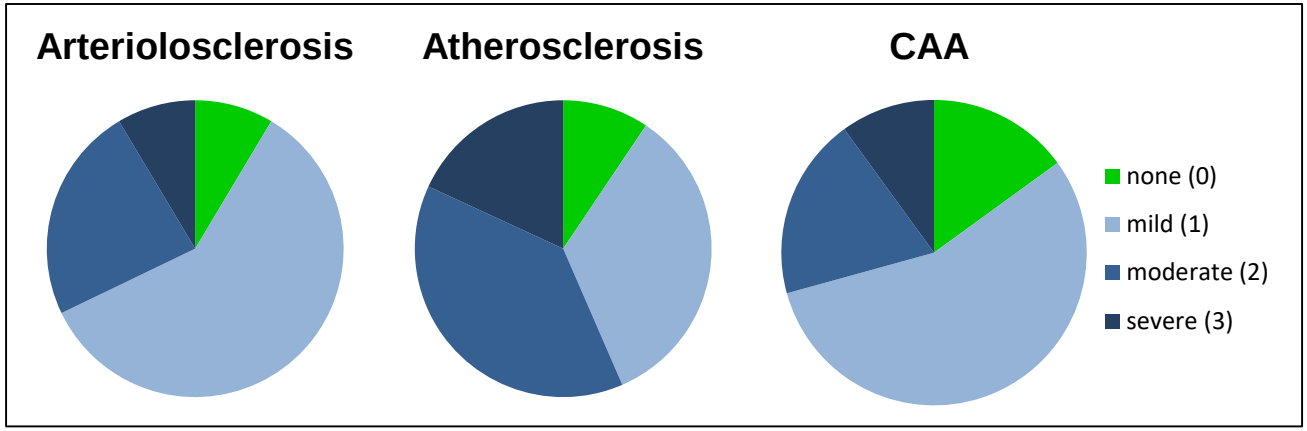


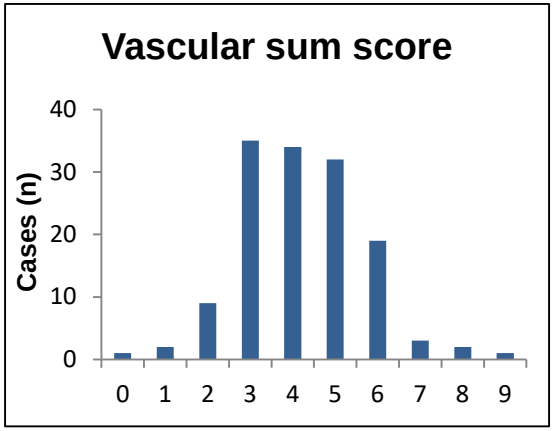


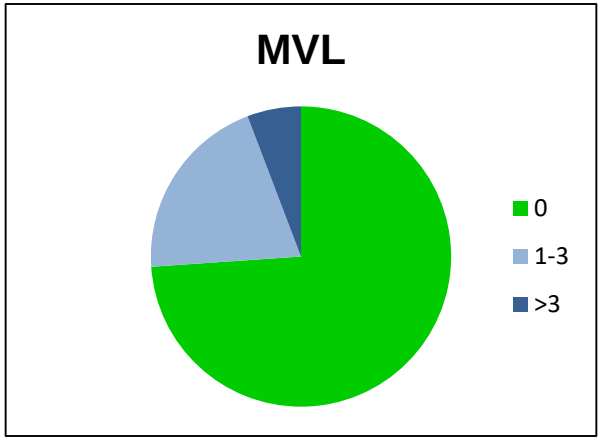


Univariate analysis

Variable		AD-P (N=59)	AD+P (N=81)	P
MVL	0 >0	63% 32%	80% 19%	0.20
Vascular sum score		4.52 (1.60)	3.99 (1.29)	0.04







Univariate analysis

Variable		AD-P (N=59)	AD+P (N=81)	P
PHF-1 tau	Volume fraction Log_2(volume fraction)	0.009 [0.0001, 0.3347] -6.86 (3.76)	0.025 [0.0002, 0.3294] -5.30 (2.84)	0.01
Oligomeric tau	Volume fraction Log_2(volume fraction)	0.002 [0.0001, 0.0418] -9.22 (2.37)	0.003 [0.0002, 0.0402] -8.57 (2.08)	0.10
Aβ	Volume fraction Log_2(volume fraction)	0.037 [0.0008, 0.1098] -4.76 (1.34)	0.037 [0.0018, 0.1298] -4.76 (1.15)	0.99
HLA-DR	Volume fraction Log_2(volume fraction)	0.006 [0.0002, 0.0542] -7.40 (1.79)	0.005 [0.0001, 0.0552] -7.64 (2.12)	0.46
Iba1	Volume fraction Log_2(volume fraction)	0.025 [0.0034, 0.088] -5.31 (0.92)	0.028 [0.0044, 0.0774] -5.15 (0.92)	0.32
HLA-DR : Iba1	Volume fraction Log_2(volume fraction)	0.235 [0.0072, 7.2941] -2.09 (2.06)	0.177 [0.0024, 2.2169] -2.50 (2.20)	0.27
Lewy pathology	Positive Negative	43% 57%	56% 44%	0.20
TDP-43 pathology	Positive Negative	45% 55%	65% 35%	0.04
MVL	0 >0	63% 32%	80% 19%	0.20
Vascular sum score		4.52 (1.60)	3.99 (1.29)	0.04

Krivinko et al, Am J Psych 2018

Stepwise logistic regression

Variable	Odds ratio	p value	R^2
PHF-1 tau, $\log_2$(volume fraction):	1.16	0.01	0.07
TDP-43 pathology, positive	2.22	0.04	0.05
HLA-DR : Iba1, $\log_2$(volume fraction ratio)	0.85	0.08	0.01
Microvascular lesion count, >0	0.56	0.21	0.04
Vascular Sum Score	0.80	0.11	0.04
Total Variance Explained			**0.18**

Krivinko et al, Am J Psych 2018

Synaptic proteome

- **Liquid chromatography-mass spectrometry (LC-MS/MS)**
- **190 synaptically localized proteins**

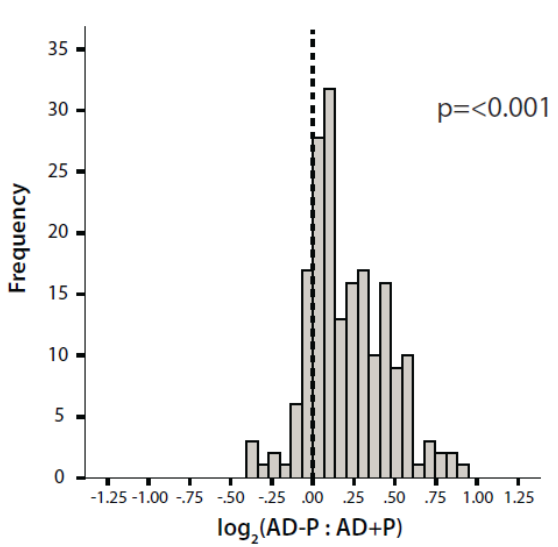
Vesicular fusion	**Energy metabolism**
Protein trafficking	**Cytoskeletal scaffolding**
Glutamate receptors	**Kinases**
Phosphatases	

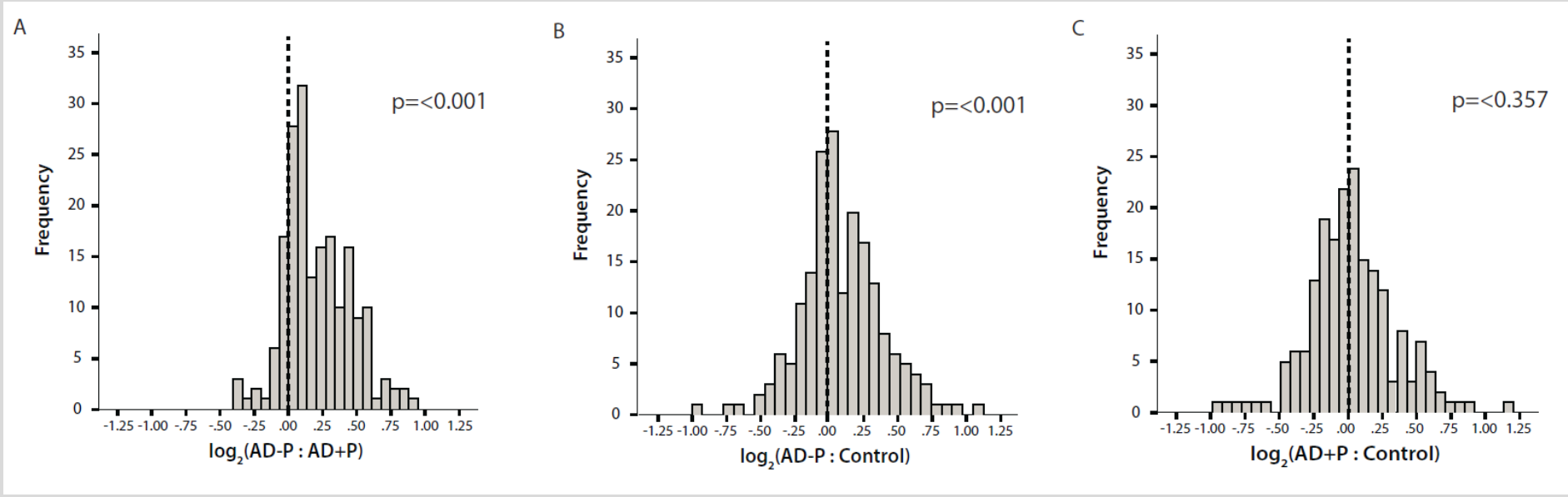
- **Dorsolateral prefrontal gray matter homogenates**
- **3 groups:**
  - **AD+P (n=38)**
  - **AD-P (n=18)**
  - **Unaffected controls (n=12)**

Synaptic proteins differentially expressed in AD+P at nominal significance (n=5)

Protein Name	Mean ratio (AD+P vs AD-P)	p
CASK (Calcium/calmodulin dependent serine protein kinase)	0.5314	0.0104
SYNGAP1 (synaptic Ras GTPase activating protein 1)	0.5517	0.0260
MTOR (mechanistic target of rapamycin kinase)	0.6757	0.0350
PRKCG (protein kinase C gamma)	0.6782	0.0409
MAP2 (microtubule associated protein 2)	0.6860	0.0435

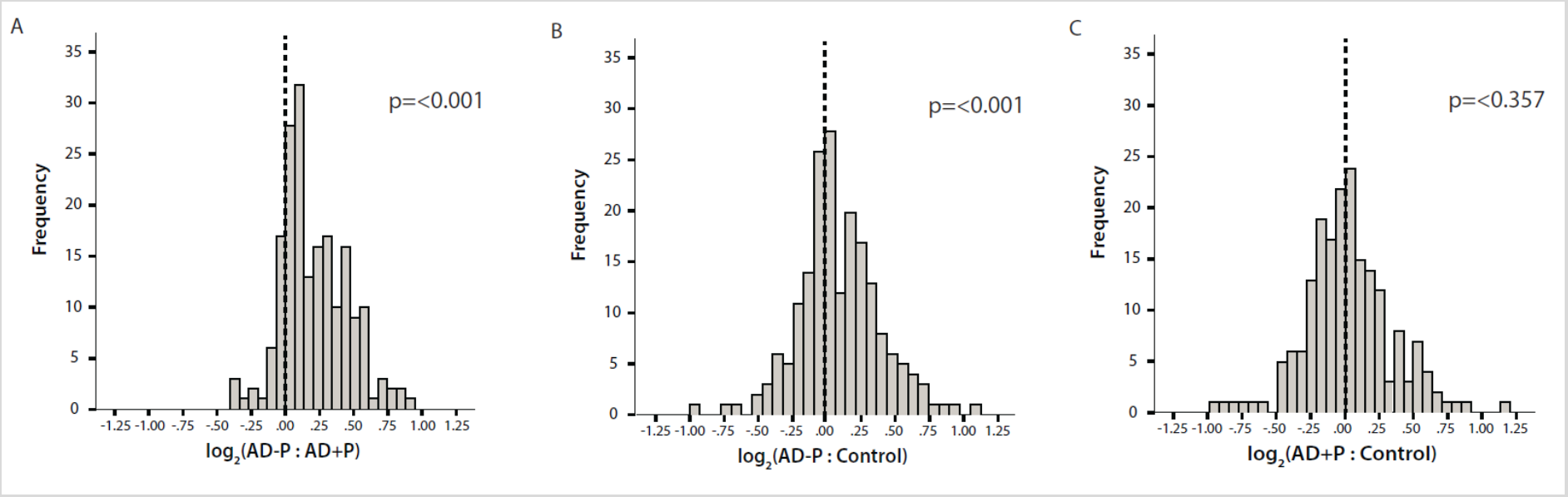
A


p=<0.001
Frequency
35
30
25
20
15
10
5
0
-1.25 -1.00 -.75 -.50 -.25 .00 .25 .50 .75 1.00 1.25
log2(AD-P : AD+P)

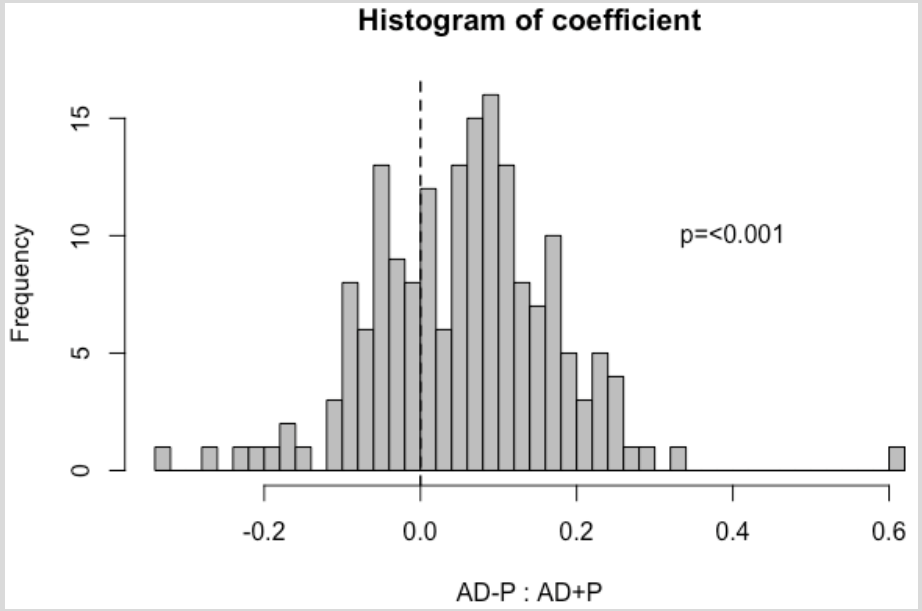


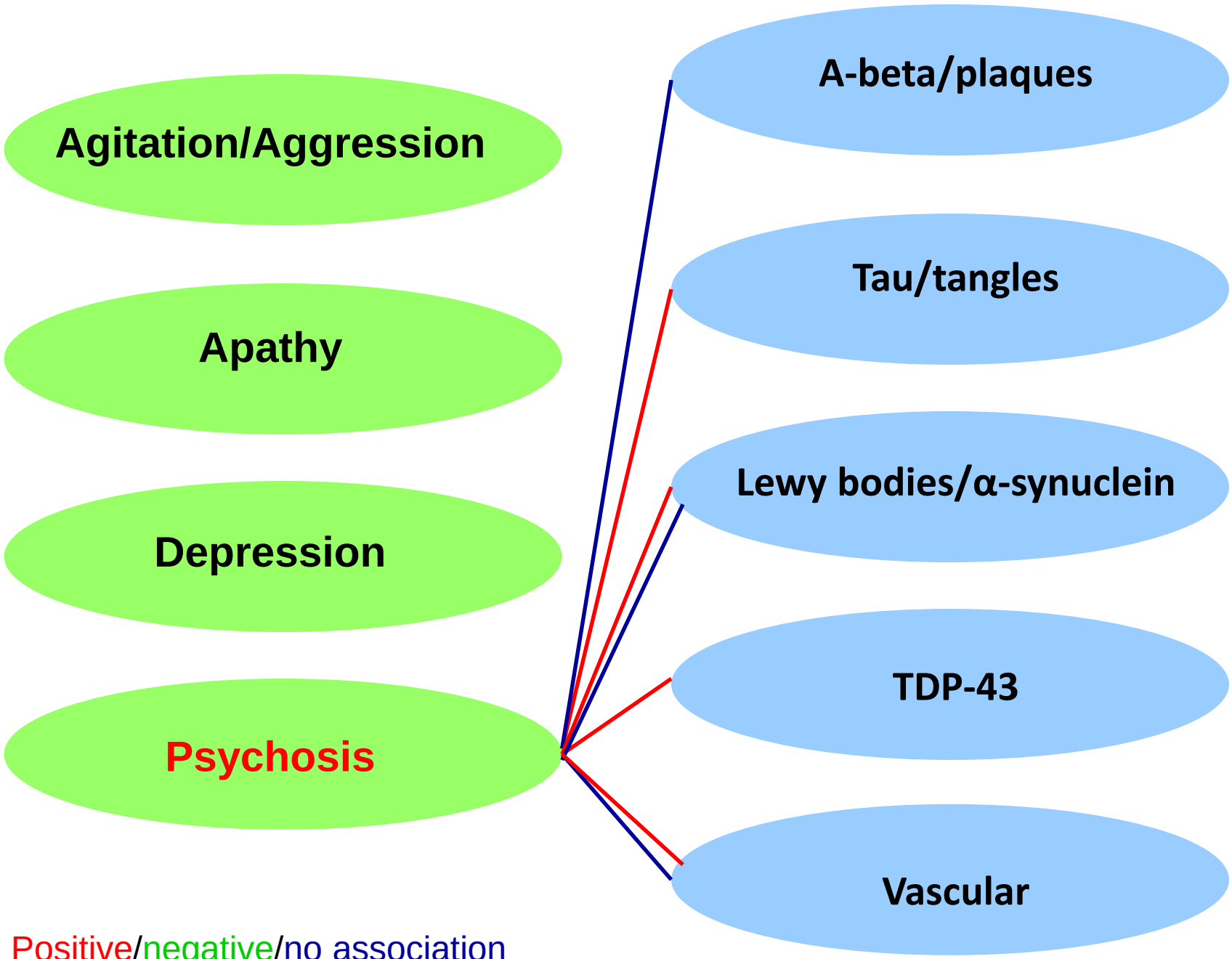
Krivinko et al, Am J Psych, under revision

Proteomics



RNAseq




Agitation/Aggression
Apathy
Depression
Psychosis
A-beta/plaques
Tau/tangles
Lewy bodies/α-synuclein
TDP-43
Vascular
Positive/negative/no association

Summary

- **BPSDs are variably associated with neuropathological disease burden**
  - **Incomplete neuropathological characterization of many phenotypes**
- **NFTs/tau burden most consistently associated with BPSDs**
  - **Quantitative measures required to detect associations**
  - **Region-specific analysis may be required**
- **TDP-43 pathology associated with psychosis and agitation/aggression**

Summary

- **Neuropathological variables predict <20% of variance in psychosis status**
- **Accumulation of synaptically expressed proteins in AD-P compared to AD+P and unaffected controls may represent signature of resilience**

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