The Neuropathology of Nondemented Aging: Evidence for Preclinical AD

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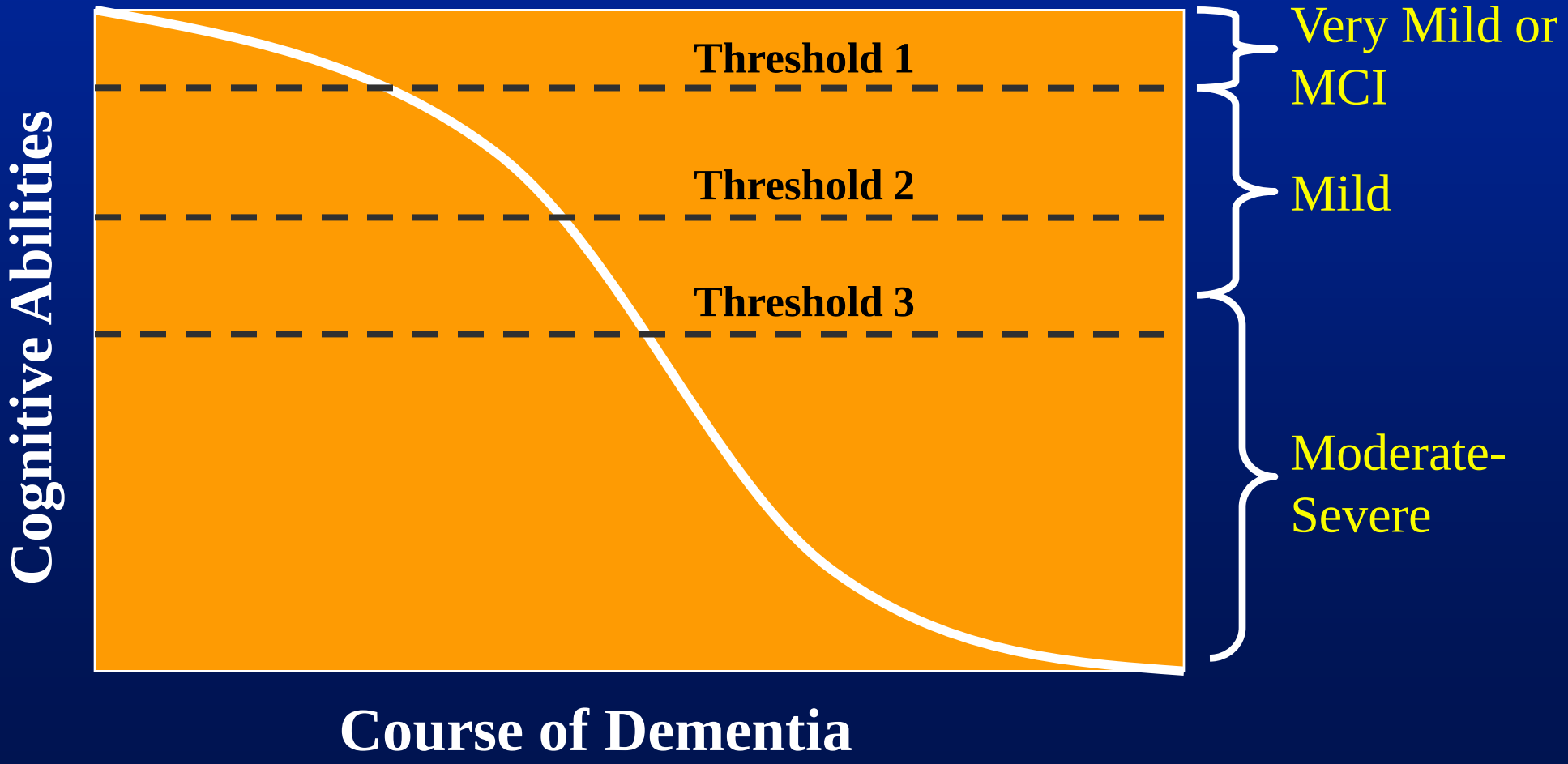
  Alzheimer's Disease & Associated Disorders

Diagnostic Thresholds for Dementia

Dementia results from progressive neuronal deterioration, from minimal to extensive. Conventional diagnosis draws a line in its course, labeling one side as demented and the other not.



Preclinical Alzheimer's Disease

- Premise: AD pathologic process operates for many years before producing symptoms (i.e., MCI/dementia)
- Key corollary: Preclinical AD is not benign; affected individuals will develop symptomatic AD if they live long enough
- Time to symptomatic AD is influenced by brain and cognitive reserve and factors yet unknown

Hypothetical relationships of aging, preclinical AD, and AD

	Aging	Preclinical AD	Very Mild AD
Plaques in neocortex	None or a few diffuse plaques	Many neuritic & diffuse plaques	Many neuritic & diffuse plaques
Tangles in entorhinal cortex & hippocampus/CA1	Few to many (increases w/age)	Many	Many
Cell loss in entorhinal cortex & hippocampus/CA1	None	Little to none	Substantial (30%-60%)
Clinical diagnosis	Normal, CDR 0	Normal, CDR 0	Very mild dementia or MCI, CDR 0.5
Pathological diagnosis	Normal	AD	AD

Price and Morris, Ann Neurol 1999;45:358-368; Price JL et al, Arch Neurol 2001;58:1395-1402

Specific Aims: Neuropathology of Nondemented Aging

- To document the frequency of histopathologic AD in nondemented aging (preclinical AD)

- To compare the cognitive status of nondemented cases, with and without histopathologic AD, and determine whether AD pathology can be truly presymptomatic

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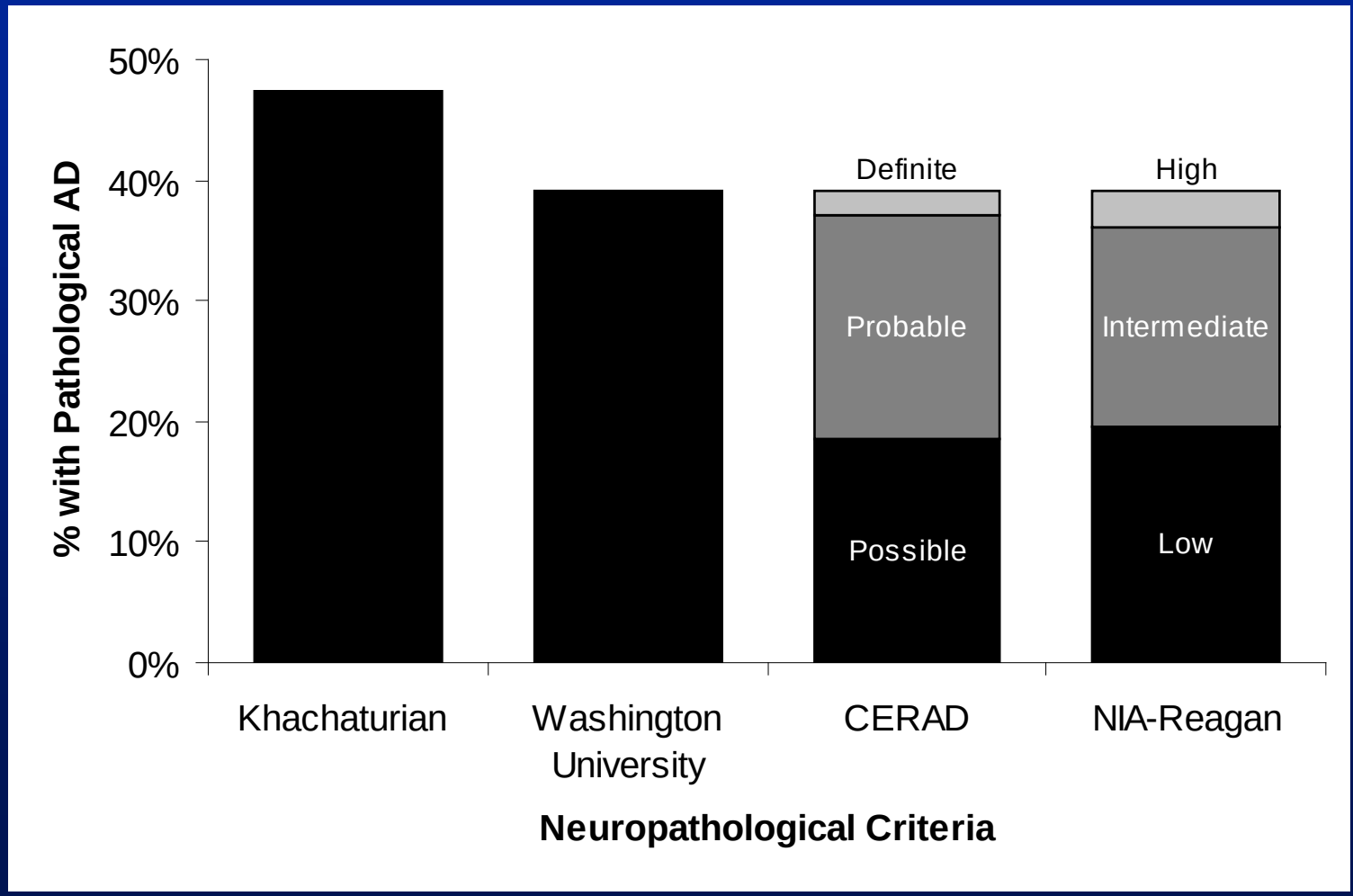
Study Design

- Nondemented individuals, assessed clinically and cognitively within 2y of autopsy
- Uniform neuropathological assessment at Washington University (Daniel McKeel, MD; Joseph L. Price, PhD)
- 7 Alzheimer's Disease Centers contributed cases (n=97)
  - Washington University (18 cases)
  - Mayo Clinic (16 cases)
  - University of Kentucky (20 cases)
  - Duke University (16 cases)
  - University of Rochester (4 cases)
  - University of California, San Diego (14 cases)
  - Oregon Health Sciences (9 cases)

The CERAD and NIA-Reagan criteria agree along their ordinal scales; when dichotomized as "no AD" versus "any AD" (inc "possible/low"), they also agree with Washington University criteria.



Price JL et al, Neurobiol Aging 2009;30:1026-1036

Adjusted mean scores for 97 nondemented participants with and without neuropathological AD

	No AD (n=59)			AD (n=38)			
Variable	**N**	**Mean**	**SE**	**N**	**Mean**	**SE**	**Prob.**
Age at death (y)	59	83.7	1.4	38	85.1	1.6	.434
Interval (y) from last assessment to death	59	0.7	0.1	38	0.7	0.1	.405
Education (y)	59	15.1	0.6	37	15.7	0.6	.271
MMSE	44	28.2	0.3	30	28.1	0.4	.847
Logical Memory Delayed	18	22.1	5.0	11	22.5	5.2	.879
Boston Naming	31	54.0	0.9	23	54.1	1.1	.945
Trails A	37	46.2	8.9	25	50.6	9.2	.549
Trails B	29	102.0	15.3	18	115.0	16.1	.294
Category Fluency	36	16.7	0.9	23	15.5	1.2	.439
Digit Symbol	16	33.5	3.1	13	35.3	3.2	.699

SE = Standard Error

Age at death: 67y-105y, mean=84y; 42M, 55F. No differences in cognitive function for any neuropath criteria. Caveat: missing data for many variables. Price JL et al, Neurobiol Aging

Correlation of AD Lesions with Cognitive Performance

	Amyloid burden (neocortical)	Diffuse SPs (neocortical)	Diffuse SPs (limbic)	NFTs (neocortical)	NFTs (limbic)
Logical Memory	**.526***	**.541***	**.584***		
Trails A	**.500*****	**.377***			
Trails B			**.405***		
Category Fluency				**.557***	
MMSE					**.359****

*p <.05, ** p< .01, *** p<.001

Price JL et al, Neurobiol Aging 2009;30:1026-1036

Interpretations

- A preclinical stage of AD occurs in up to 40% of older adults, unaccompanied by detectable cognitive impairment
- SPs, amyloid burden, and NFTs are associated with subclinical cognitive dysfunction, indicating the pathobiological relevance of even diffuse SPs
- NFTs in nondemented individuals appear to accumulate as a function of age; SPs appear to be age-independent
- It remains unknown whether individuals with preclinical AD are destined to develop dementia if they live sufficiently long

PIB MCBP Predicts Development of Dementia (CDR 0.5) in Cognitively Normal Individuals

	HR	CI		P value
		Lower	Upper	
Dementia (n=23)				
MCBP	2.74	0.59	12.78	0.20
Age (y)	1.11	1.04	1.18	0.002
DAT (n=9)				
MCBP	4.82	1.22	19.01	0.02
Age (y)	1.14	1.02	1.28	0.03

Morris JC et al, Arch Neurol in press