Collaborative work on:

Pre-clinical Alzheimer's disease;

Primary age-related tauopathy (PART)

Team:

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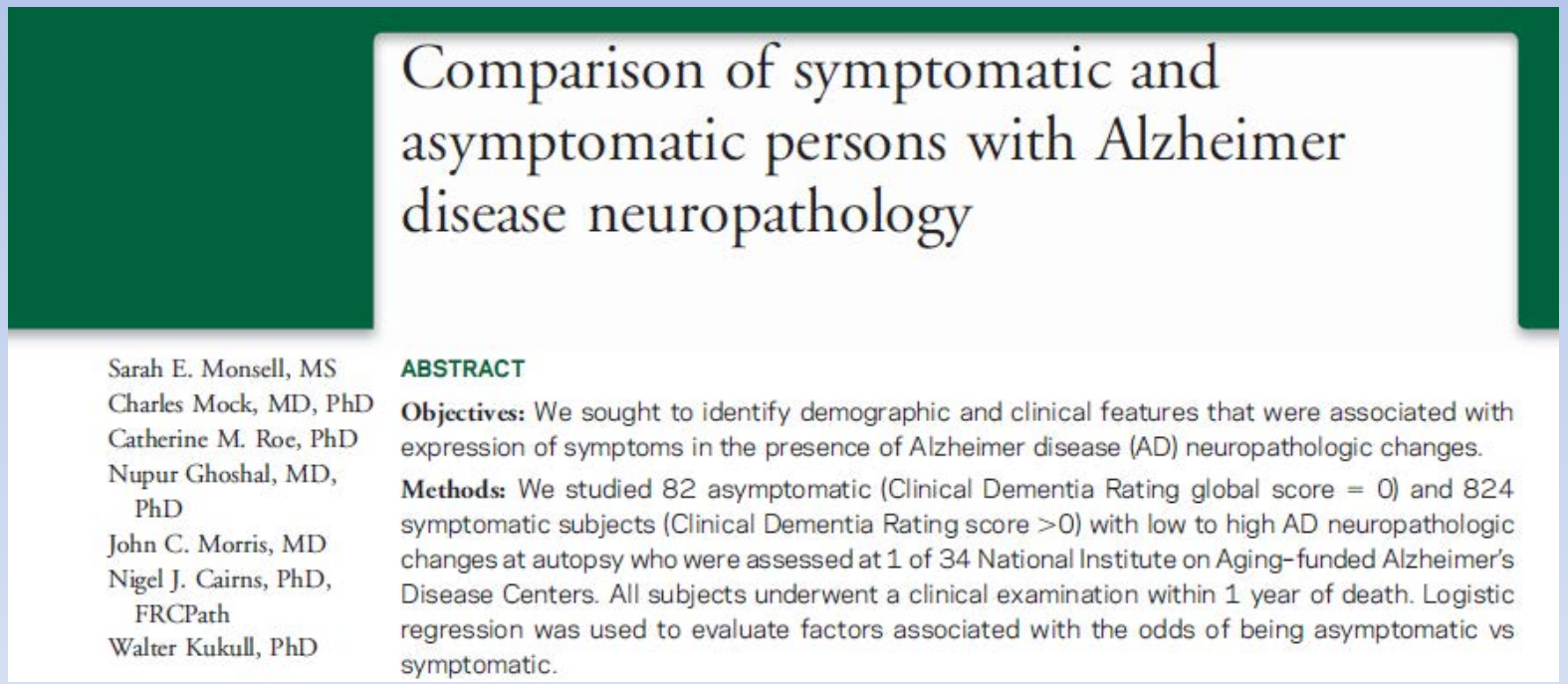
Characteristics of asymptomatic persons with AD neuropathology as defined by the NIA-AA Guidelines



Comparison of symptomatic and asymptomatic persons with Alzheimer disease neuropathology

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ABSTRACT

Objectives: We sought to identify demographic and clinical features that were associated with expression of symptoms in the presence of Alzheimer disease (AD) neuropathologic changes.

Methods: We studied 82 asymptomatic (Clinical Dementia Rating global score = 0) and 824 symptomatic subjects (Clinical Dementia Rating score >0) with low to high AD neuropathologic changes at autopsy who were assessed at 1 of 34 National Institute on Aging–funded Alzheimer's Disease Centers. All subjects underwent a clinical examination within 1 year of death. Logistic regression was used to evaluate factors associated with the odds of being asymptomatic vs symptomatic.

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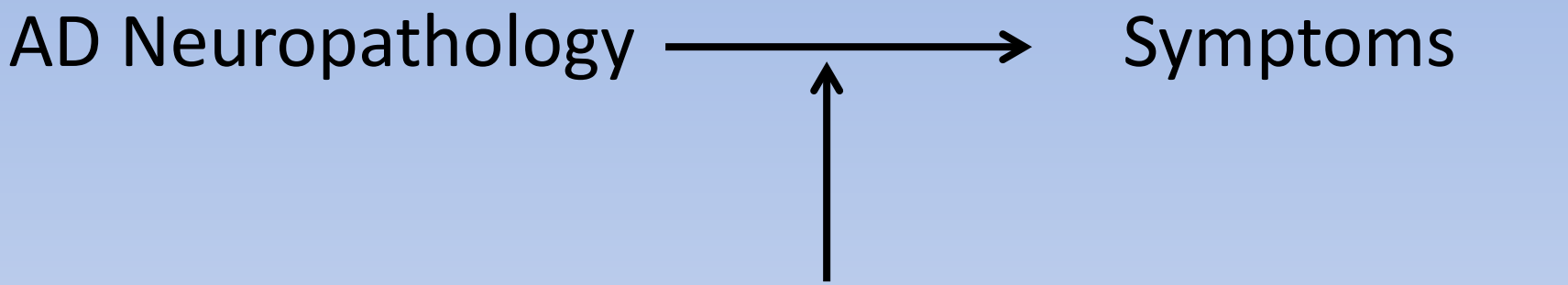

Demographics

Genetic status

Comorbid conditions (e.g. vascular disease)

Environmental influences

Cognitive reserve

Acta Neuropathol (2012) 123:1–11
DOI 10.1007/s00401-011-0910-3

CONSENSUS PAPER

National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach

Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman

Table 2 "ABC" score for AD neuropathologic change

"A"	Thal Phase for Aβ plaques [57]	"B"	Braak and Braak NFT stage [14,15]	"C"	CERAD neuritic plaque score [41]
0	0	0	None	0	None
1	1 or 2	1	I or II	1	Sparse
2	3	2	III or IV	2	Moderate
3	4 or 5	3	V or VI	3	Frequent

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Table 3 "ABC" score for level of AD neuropathologic change

AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

Inclusion:

A: Thal phase $\geq$ 1 (any diffuse plaque)

OR

C: C $\geq$ 1 (any neuritic plaques)

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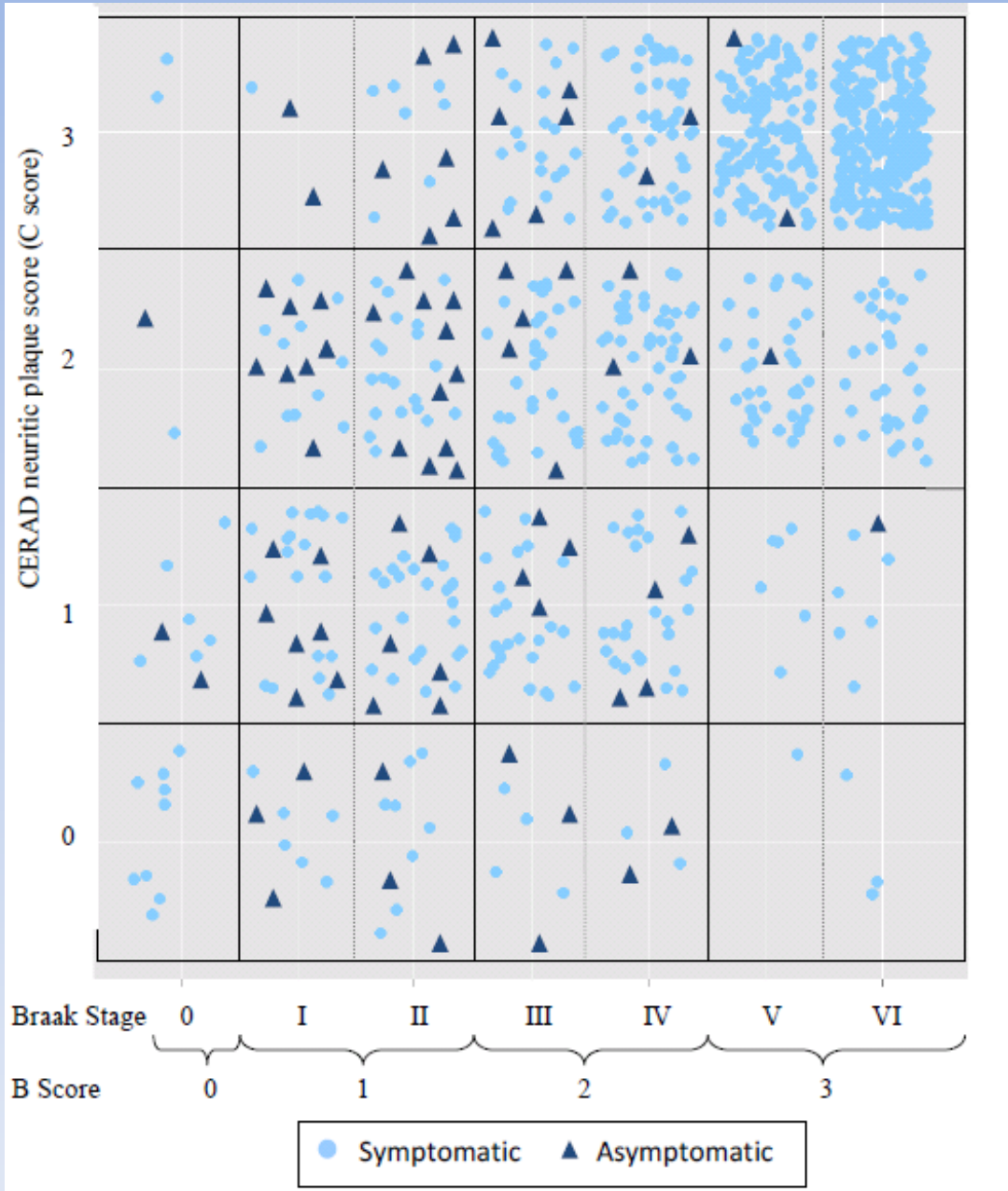
Clinical status

CDR (Clinical Dementia Rating) global score at last clinical assessment:

- 0 = asymptomatic
- 0.5 or higher = symptomatic

Scatter-plot by B and C score



893 (91.5%) CDR ≥ 0.5 (symptomatic)

83 (8.5%) CDR = 0 (asymptomatic)

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Multivariable logistic regression: odds of being asymptomatic

Predictor	OR	95% CI*
Age at last visit	**1.04**	**(1.01,1.07)**
Education (at least some college vs. no college)	1.46	(0.71,2.99)
Depression (present within the past 2 years vs. absent)	0.65	(0.33,1.26)
Sex (female vs. male)	1.21	(0.66,2.21)
Hachinski Ischemic Score	**0.82**	**(0.69.0.97)**
APOE (e4 vs. no e4)	**0.36**	**(0.16,0.83)**
B score (continuous)	**0.28**	**(0.17,0.45)**
C score (continuous)	0.92	(0.62,1.36)
Lewy body pathology (present vs. not present)	0.68	(0.24,1.97)
Amyloid angiopathy (present vs. not present)	0.69	(0.37,1.28)

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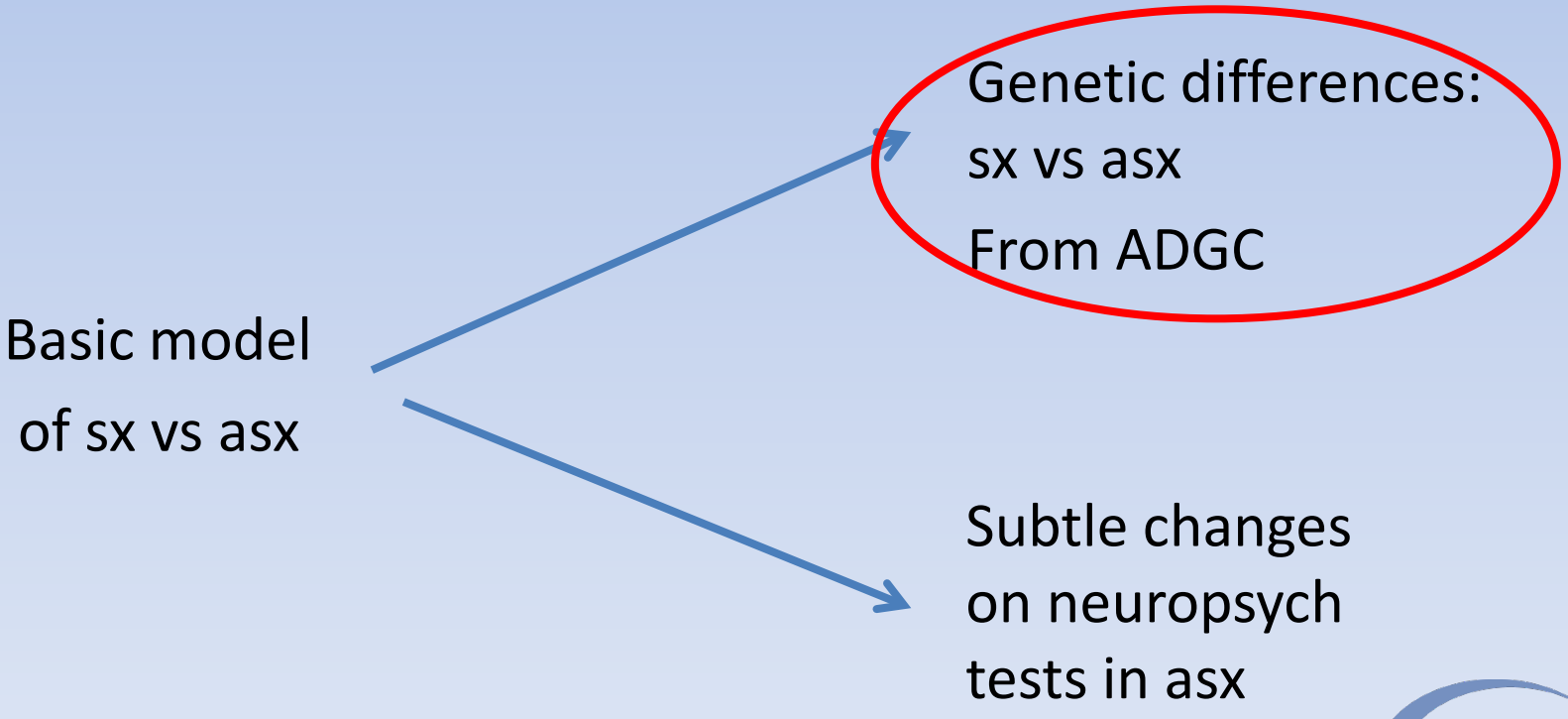
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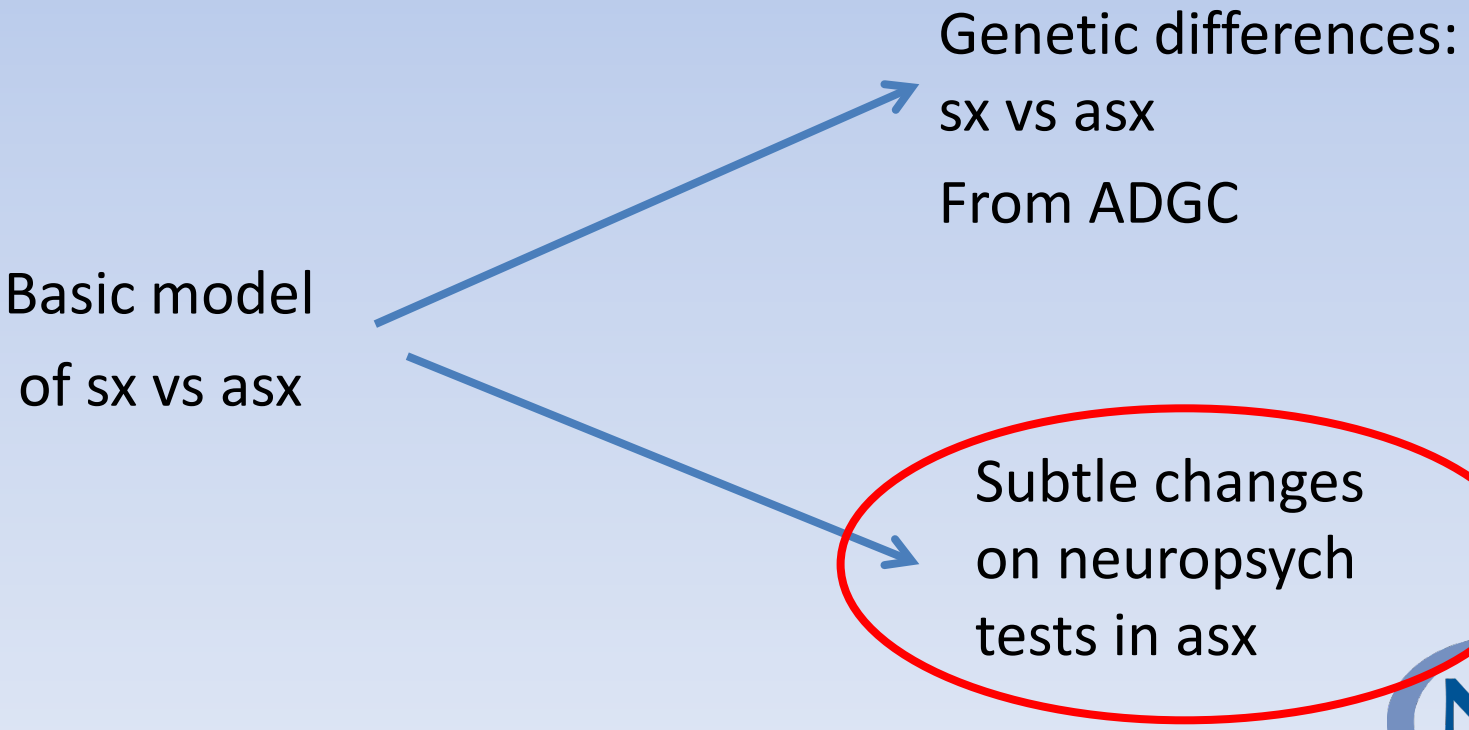
- Potential associations between **expression** of existing AD NP and other (non-APOE) loci minimally explored thus far.

- Monsell et al, ADAD, 2016

Odds ratio (adjusted for age and sex) for symptomatic AD vs. asymptomatic AD for each SNP and stratified by APOE e4 carrier status assuming an additive mode of inheritance

Gene	SNP	OR	OR in APOE e4 carriers	OR in APOE e4 non-carriers
CR1	rs6656401	1.46 (0.85,2.49)	1.56 (0.53,4.53)	1.44 (0.76,2.73)
BIN1	rs6733839	0.96 (0.63,1.46)	1.02 (0.41,2.54)	1.06 (0.65,1.75)
CD2AP	rs10948363	0.73 (0.50,1.09)	**0.35 (0.16,0.75)**	0.99 (0.62,1.61)
HLA-DRB5/HLA-DRB1	rs9271192	1.01 (0.67,1.50)	0.93 (0.41,2.11)	1.03 (0.64,1.65)
EPHA1	rs11771145	0.96 (0.65,1.41)	1.29 (0.60,2.77)	0.88 (0.56,1.38)
CLU	rs9331896	0.83 (0.55,1.25)	1.18 (0.49,2.87)	0.73 (0.45,1.19)
PTK2B	rs28834970	1.22 (0.85,1.77)	1.38 (0.66,2.88)	1.10 (0.71,1.70)
MS4A4A	rs983392	1.29 (0.88,1.90)	1.57 (0.73,3.40)	1.19 (0.75,1.90)
PICALM	rs10792832	1.16 (0.80,1.70)	1.03 (0.46,2.30)	1.15 (0.75,1.77)
SORL1	rs11218343	1.72 (0.68,4.33)	2.99 (0.76,11.75)	1.45 (0.38,5.49)
SLC24A4/RIN3	rs10498633	1.24 (0.83,1.87)	1.50 (0.66,3.43)	1.15 (0.71,1.85)
DSG2	rs8093731	0.96 (0.12,7.86)	NA	0.94 (0.11,8.20)
ABCA7	rs4147929	**1.66 (1.00,2.76)**	1.25 (0.52,3.02)	1.81 (0.97,3.40)
CD33	rs3865444	1.26 (0.87,1.83)	1.28 (0.60,2.70)	1.44 (0.93,2.23)
CASS4	rs7274581	1.12 (0.62,2.04)	1.53 (0.54,4.35)	1.03 (0.49,2.17)
NME8	rs2718058	0.77 (0.51,1.15)	0.89 (0.40,2.02)	0.74 (0.46,1.19)
CELF1	rs10838725	0.99 (0.67,1.46)	0.70 (0.34,1.46)	1.14 (0.70,1.85)
FERMT2	rs17125944	1.69 (0.76,3.74)	3.05 (0.39,23.66)	1.41 (0.58,3.40)
INPP5D	rs35349669	0.88 (0.61,1.28)	1.07 (0.50,2.27)	0.75 (0.49,1.15)
MEF2C	rs190982	1.24 (0.84,1.82)	1.03 (0.45,2.36)	1.15 (0.74,1.80)
ZCWPW1	rs1476679	1.31 (0.87,1.96)	**2.98 (1.33,6.69)**	1.04 (0.63,1.70)
MAPT	rs393152	**2.18 (1.26,3.75)**	**3.73 (1.27,10.97)**	1.77 (0.93,3.40)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Performance on neuropsychological tests.

- ***Specific aims:***
- 1. To determine whether persons with AD neuropathologic change and CDR global score of 0 have more subtle changes that are detectable by neuropsychological tests.
- 2. To determine the trajectory of these changes over time.

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Neuropsychological changes in asymptomatic persons with Alzheimer disease neuropathology

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John C. Morris, MD
Walter Kukull, PhD

ABSTRACT

Objective: To determine whether asymptomatic persons with Alzheimer disease (AD) neuropathologic change differ in the trajectory of their cognitive performance compared to asymptomatic persons without AD neuropathologic change.

Methods: Longitudinal performance on standard neuropsychological tests was examined in participants who died within 2 years of their last cognitive assessment and who were never diagnosed with mild cognitive impairment or dementia (Clinical Dementia Rating global score of 0 at all assessments). Using cognitive and neuropathologic data collected between 2005 and

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ORIGINAL ARTICLE

Neuropsychological Markers of Cognitive Decline in Persons With Alzheimer Disease Neuropathology

Jason Hassenstab, PhD, Sarah E. Monsell, MS, Charles Mock, MD, PhD, Catherine M. Roe, PhD, Nigel J. Cairns, PhD, FRCPath, John C. Morris, MD, and Walter Kukull, PhD

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Cognitive Measures

- Cognitive Composites of UDS Measures

  (Hayden et al. 2011 *ADAD*)

  - ***Episodic Memory:*** WMS-R Logical Memory Immediate & Delayed Recall
  - ***Language:*** Boston Naming Test, Animal Naming, Vegetable Naming
  - ***Attention & Working Memory:*** WMS-R Digit Span Forward & Backwards
  - ***Executive Function***: Trailmaking Test Parts A & B, WAIS Digit-Symbol
  - ***Global Composite:*** All measures above

Monsell et al., 2014 *Neurology*

- 211 participants who were never symptomatic (CDR 0), but died with significant levels of AD neuropathology (n=131), or who had no evidence of AD neuropathology (n=80)
- Working memory/Attention declined faster in AD-NP.

Domain	No. of subject-visits	Annual mean change for AD-NP (95% CI)[a,b]	Annual mean change for non-AD-NP (95% CI)[a,b]	Annual mean difference between AD-NP and non-AD-NP (95% CI)[a]	*p* Value[a]
Episodic memory	565	0.08 (−0.09, 0.25)	0.17 (0.08, 0.25)	−0.09 (−0.19, 0.02)	0.10
Language	553	−0.04 (−0.18, 0.09)	0.02 (−0.04, 0.08)	−0.07 (−0.15, 0.01)	0.11
Attention	573	−0.09 (−0.23, 0.06)	0.02 (−0.05, 0.09)	−0.11 (−0.19, −0.02)	0.02
Executive function	538	−0.02 (−0.24, 0.19)	0.01 (−0.09, 0.12)	−0.03 (−0.16, 0.09)	0.60
Global composite	511	−0.02 (−0.15, 0.12)	0.06 (−0.01, 0.13)	−0.08 (−0.15, 0.00)	0.06

Abbreviations: AD = Alzheimer disease; CDR = Clinical Dementia Rating; CI = confidence interval; NP = neuropathologic.

[a] Adjusted for age at visit; education; sex; presence of ischemic, hemorrhagic, or vascular pathology; presence of cerebral amyloid angiopathy; and presence of Lewy body pathology.

[b] Interpretation: a negative mean annual change indicates a decline in cognition, whereas a positive slope indicates improvement in scores over time.

Significance

- Attention/working memory as earliest changes in preclinical AD
  - Balota et al, Psychol Aging, 2010
  - Tse et al, Neuropsychology, 2010
  - Storandt et al, Arch Neurol, 2009

- Subtle changes in preclinical AD more likely to be detected by changes over time
  - Knopman et al, Neurodegener Dis Manag 2012
  - Riley et al, J Alz Dis, 2011

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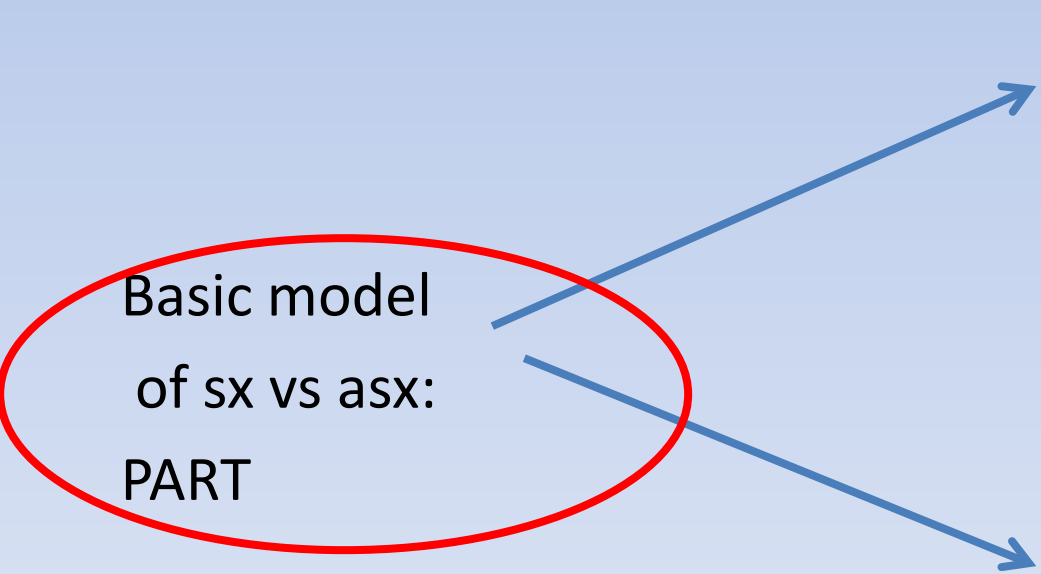
Extension of similar approach to PART



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Primary Age-Related Tauopathy (PART)

- BROAD GOALS: To better characterize PART and to facilitate differentiation from other tauopathies, especially AD.

- SPECIFIC AIMS: To characterize clinical and neuropathological features associated with cognitive impairment in participants with:
  - no neuritic amyloid plaques (PART definite)
  - sparse neuritic plaques (amyloid sparse / PART possible).

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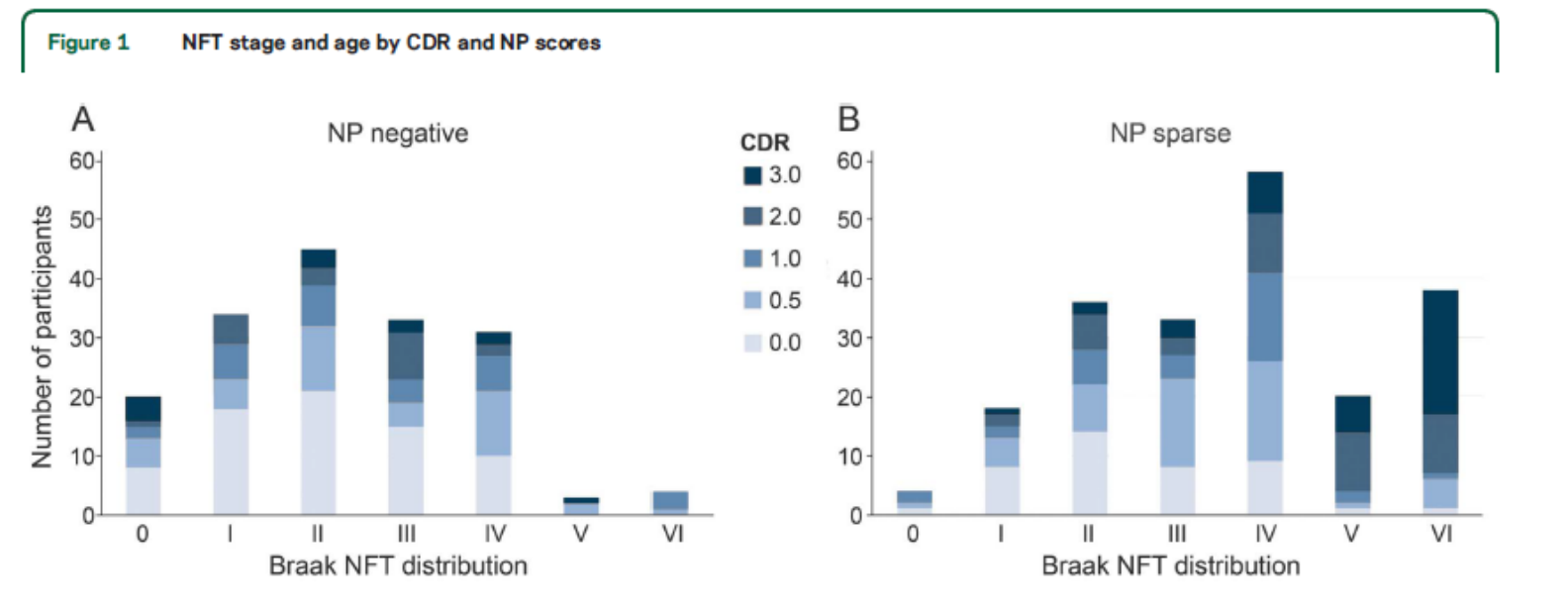
PART definite

Amyloid sparse



PART definite (Neuritic plaque negative) *n*=170
Amyloid sparse (Neuritic plaque sparse) *n*=207

PART definite:

- Less likely to have Braak stage V or VI
  - (4% for PART definite; 28% for NP sparse)*
- Less likely to be symptomatic (CDR > 0).
  - (58% for PART definite; 80% for NP sparse)*

*p<0.001

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Independent predictors of sx status

- PART definite:
  - Depression (aOR: 4.20; CI: 2.15-8.19);
  - Braak stage (aOR: 1.42; CI: 1.04-1.95);
  - History of stroke (aOR: 8.09; CI: 2.63-24.82).

- Amyloid sparse group:
  - Education (aOR: 0.80; 95% CI: 0.65-0.99);
  - Braak stage (aOR: 1.91; 95% CI: 1.07-3.43);
  - Amyloid angiopathy (aOR: 2.75; 95% CI: 1.14-6.64).

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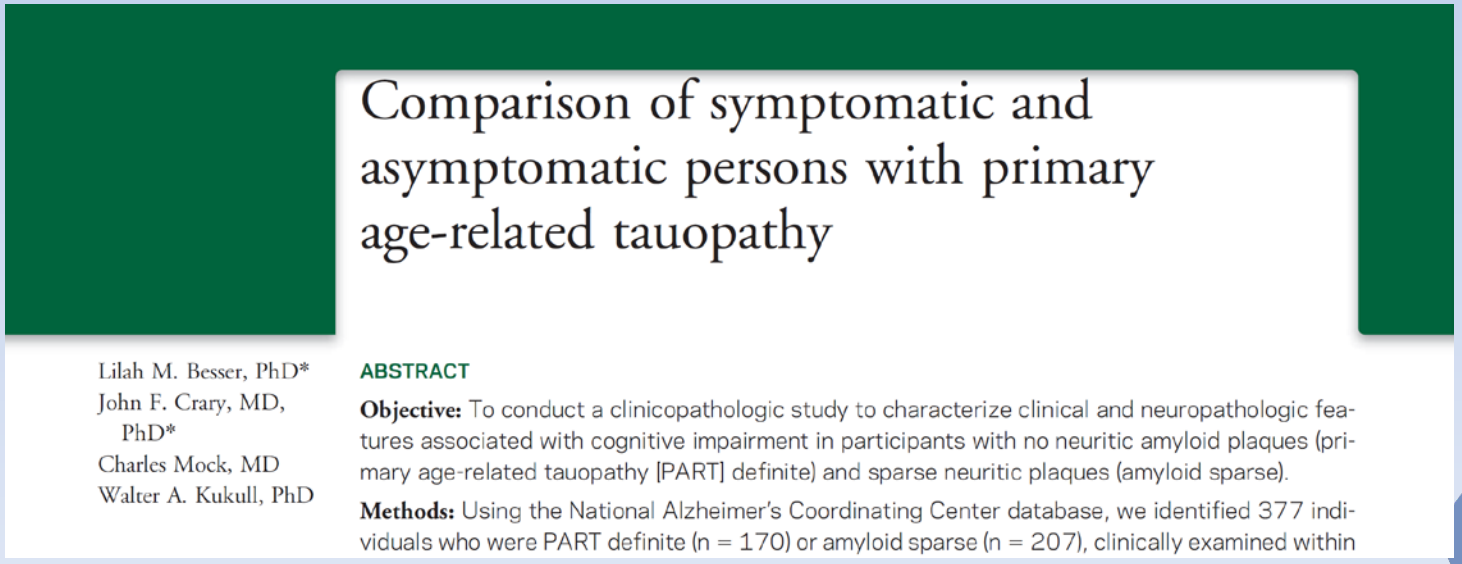
Conclusions (PART)

These findings support the hypothesis that participants with PART have an amyloid-independent dementing AD-like temporal lobe tauopathy.



Comparison of symptomatic and asymptomatic persons with primary age-related tauopathy

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Charles Mock, MD
Walter A. Kukull, PhD

ABSTRACT

Objective: To conduct a clinicopathologic study to characterize clinical and neuropathologic features associated with cognitive impairment in participants with no neuritic amyloid plaques (primary age-related tauopathy [PART] definite) and sparse neuritic plaques (amyloid sparse).

Methods: Using the National Alzheimer's Coordinating Center database, we identified 377 individuals who were PART definite (n = 170) or amyloid sparse (n = 207), clinically examined within

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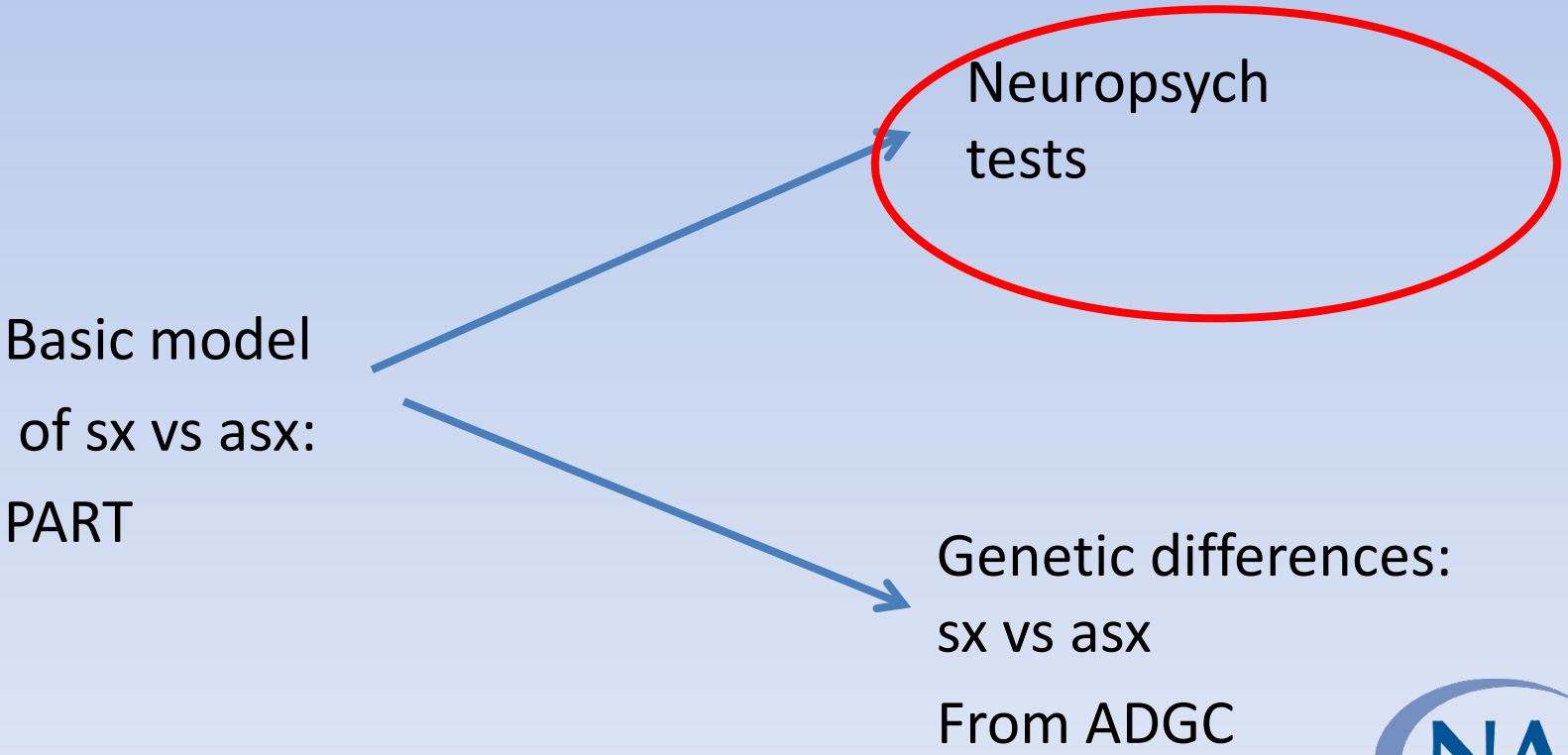
Extension of similar approach to PART



Conclusions: NACC collaboration with ADCs

- ADCs: use UDS data by themselves.
- Smaller #: consultation with NACC staff.
- Develop ideas collaboratively.

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