

Neurología de la conducta y Neuropsicología Basadas en la Evidencia

Jordi Peña-Casanova, MD, D.Npsic.

Institut Municipal d'Assistència Sanitària. Hospital del Mar

Master de Neuropsicologia

Universitat Autònoma de Barcelona

Dept. de Psiquiatria i Med. Legal

Selección y actualización de diapositivas para las
clases impartidas en el curso

NEUROBIOLOGIA DE LA CONDUCTA,
FUNDAMENTOS Y AVANCES RECIENTES

Guadalajara, Jal. México

5-9 de diciembre de 2005

Evidence Based Medicine

GENERAL PRINCIPLES

Evidence Based Medicine (EBM): Definitions

- An approach to practicing medicine in which the clinician is *aware of the evidence* in support of her clinical practice, *and the strength of that evidence*.
- The process of *systematically finding, appraising, and using contemporaneous research findings* as the basis for clinical decisions.
- The conscientious, explicit and judicious *use of current best evidence in making decisions* about the care of individual patients

EBM

- De-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making...
- Stresses the examination of evidence from clinical research
- Requires new skills of the physician...

TWO BASIC REFERENCES

Evidence-Based Medicine Working Group. **Evidence-Based Medicine. A New Approach to Teaching the Practice of Medicine.** JAMA, 268:2420-2425, 1992

Pallie W, Carr DH. **The McMaster Medical Education Philosophy in Theory, Practice and Historical Perspective.** Medical Teacher, 9:59-71, 1987.

The Former Paradigm, I

1. Unsystematic observations from clinical experience are a valid way of building and maintaining one's knowledge about patient prognosis, the value of diagnostic tests, and the efficacy of treatment.
2. The study and understanding of basic mechanisms of disease and pathophysiologic principles are a sufficient guide for clinical practice.

The Former Paradigm, II

3. A combination of thorough¹ traditional medical training and common sense is sufficient to allow one to evaluate new tests and treatments.
4. Content expertise and clinical experience are sufficient base from which to generate valid guidelines for clinical practice.

1. Minucioso, completo, concienzudo...

The New Paradigm, I

1. Clinical experience .../... **Systematic attempts to record observations in a reproducible and unbiased fashion** markedly increase the confidence one can have in knowledge about patient prognosis, the value of diagnostic tests, and the efficacy of treatment. In the absence of systematic observation **one must be cautious in the interpretation of information derived from clinical experience and intuition**, for it may at times be misleading.

The New Paradigm, II

2. The study and understanding of basic mechanisms of disease are necessary but insufficient guides for clinical practice. **The rationales for diagnosis and treatment, which follow from basic pathophysiologic principles, may in fact be incorrect, leading to inaccurate predictions about the performance of diagnostic tests and the efficacy of treatments.**

The New Paradigm, III

3. Understanding certain rules of evidence is necessary to **correctly interpret literature** on causation, prognosis, diagnostic tests, and treatment strategy. .../...

*Clinicians must be ready to accept and live with **uncertainty** and to acknowledge that management decisions are often made in the face of relative ignorance of their true impact*

The new paradigm puts a much lower value on authority

Physicians whose practice is based on an understanding of the underlying evidence will provide superior patient care

EBM:El problema de los libros

- Algunos temas están frecuentemente obsoletos
 - El libro “nace viejo”
- Errores
 - Recomendaciones no contrastadas
- Sesgos (Biases)
 - Prejuicios del autor/es
 - Ejemplo: Recomendaciones de test

EBM & EBNpsic: Skills involved

- Defining **clinical questions** in a way that allows **clear answers**
- Efficient **searching for the best information** to answer the question
- **Appraising** the evidence to determine its strength
- Extracting the **clinical message** from the information
- **Applying** that information to ones' patients

EBM

SEARCHING THE BEST
EVIDENCES

Revisiones sistemáticas de la evidencia científica: motivos, I

- 1.- Variabilidad en los estilos de práctica clínica: necesidad de especificar criterios de idoneidad
- 2.- Variación en la utilización de recursos sanitarios
- 3.- Aumento del gasto sanitario: necesidad de una gestión más eficiente de los recursos
- 4.- Exceso de información científica que no puede ser analizada ni asimilada con celeridad por los profesionales

Revisiones sistemáticas de la evidencia científica: motivos, II

- 6.- Existencia de influencias extrañas de base científica no demostrada.
- 7.- Falsas presunciones fisiopatológicas: hipótesis no contrastadas mediante estudios científicos de elevado rigor metodológico.
- 8.- Aumento creciente de la demanda de servicios sanitarios: necesidad de encontrar el equilibrio entre los criterios de equidad, eficiencia y calidad

“Databases” / Indices bibliográficos

- La información en el campo de la salud estaba bien organizada antes de la aparición de internet
- En la red hay mucha información, buena, regular y mala.
- Existe diversos recursos de búsqueda. No todos son buenos
- Necesidad de desarrollar criterios y “filtros” de la masiva información
- Proyecto OMNI (Organising Medical Networked Information)
 - Criterios de evaluación de recursos médicos en internet
 - <http://omni.ac.uk>
- Medline.

The National Library of Medicine

- Medline
- 1997: Accesible a través de dos interfaces de la NLM:
 - PubMed: <http://www.ncbi.nlm.nih.gov/PubMed/>
 - Internet Grateful Med: <http://igm.nlm.nih.gov/>
- Servicios privados comercializan aspecto de labase de datos
 - OVID. <http://www.ovid.com/>

Prácticas clínicas: coste y beneficio

- *“Los gestores de la sanidad que deseen alentar a los médicos a aplicar las prácticas clínicas que tengan mejor balance entre coste y beneficio deben afrontar un gran problema: los mismos médicos -por no mencionar a los técnicos ministeriales- frecuentemente **no saben cuáles son, entre tantas, las prácticas más eficaces**” (Cochrane)*

Cochrane (1979)

- *“Con toda seguridad, puede criticarse a nuestra profesión porque no hayamos organizado un resumen crítico, por especialidad o subespecialidad, adaptando periódicamente, de todos los ensayos clínicos controlados que son relevantes”*
- Cochrane falleció en 1988, y en 1992 sus discípulos dieron su nombre a una ambiciosa iniciativa internacional...

La Colaboración Cochrane

- Iniciativa internacional en EBM: Objetivo: realizar y promover la accesibilidad y las revisiones sistemáticas.
- Su logo: todo un ejemplo

Colaboración Cochrane: Logotipo

- Ilustra la revisión de siete ensayos clínicos controlados (ECC). Tratamiento corto y barato de corticosteroides dados a mujeres que con riesgo de adelantar prematuramente el parto.
 - Línea horizontal: resultado de un ensayo. Cuanto más corta más cierto el estudio.
 - Línea vertical: posición alrededor de la cual las líneas horizontales se concentrarían si los dos tratamientos comparados tuviesen efectos similares.
- El tratamiento reduce entre un 30% y un 50% la probabilidad de muerte de los recién nacidos

The Cochrane Library, I

- Ofrece un acceso rápido y sencillo a evidencias de alta calidad sobre los efectos -tanto beneficiosos como perjudiciales- de la atención sanitaria. Se actualiza cada tres meses.
- Incluye:
 - Base de datos Cochrane de revisiones sistemáticas (The Cochrane Database of Systematic Reviews-CDSR),
 - Base de datos de Resúmenes de revisiones de efectividad: The Database of Abstracts of reviews of Effectiveness-DARE
 - Registro Cochrane de Ensayos Clínicos Controlados (The Cochrane Controlled Trials Register-CCTR)

The Cochrane Library, II

- Acceso libre a resúmenes:
<http://hiru.mcmaster.ca/cochrane/cochrane/reabstr/abstract.htm/>
- Toda la información de evaluaciones críticas y resúmenes estructurados de revisiones sistemáticas.
Manual: *Cochrane Handbook*, glosario, contactos entre grupos...
- Información adicional: Revisiones sobre metodología o la guía *Netting the Evidence*

Quality of evidence ratings for therapeutic modalities (AAN)

- Class I: Evidence provided by one or more well-designed randomized, controlled clinical trials.
- Class II: Evidence provided by one or more well-designed clinical studies such as case control. Cohort studies, etc. (II.1, II.2, II.3)
- Class III: Evidence provided by expert opinion, nonrandomized historical controls, or reports of one or more.

Strength of the recommendations (AAN)

- **Type A:** Strong positive recommendations, based on Class I evid., or overwhelming Class II evid. when circumstances preclude randomized clinical trials.
- **Type B:** Positive recommendation, based on Class II evid.
- **Type C:** Positive recommendation, based on Class III evid.
- **Type D:** Negative recommendation, based on inconclusive or conflicting Class II evidence.
- **Type E:** Negative recommendation, based on evid. of ineffectiveness or lack of efficacy, based on Class II or Class I evid.

EBM: Example 1

Selected Medical Subject Headings
(MeSH)

AD: Some Clinical Questions...

- Is there cognitive impairment?
 - What is the best approach?
 - What are the evidences about sensitivity and reliability of a test... (Psychometric characteristics)?
- What is the cognitive pattern of the patient?
 - What are the preserved and impaired cognitive abilities?
 - What evidences? statistical significance vs. effect sizes?
- Are the clinical cognitive findings compatible with...?

Search

- **Medical Subject Headings (MeSH):**

 - Alzheimer's disease AND Neuropsychological test AND
Diagnosis AND Sensitivity AND Specificity AND

- **Date:** December 3, 1999

- **Result:** 108 papers

 - More frequent papers: Cognitive screening with brief tests
 - » CDT, 7-min Screen, MMSE
 - Memory
 - Comparison of screening tools
 - Neuropsychology vs. neuroimaging

CDT (Clock Drawing Test)

- Royal DR, Mulroy, Chiodo et al. (1999)
 - » Executive functions
- Brodaty & Moore (1997)
 - » Three scoring methods
- Gruber, Varner, Chen et al (1997)
 - » Comparison with the Pfeiffer Short Portable Mental Status Q
- Cacho, García, Arcaya et al (1999)
 - » Proposal: scoring method
- Mendez, Ala, Underwood (1992)
 - » Development of scoring criteria
- Esteban-Santillán, Praditsuwan et al (1998)
 - » In very mild DTA
- Wolf-Klein, Silverstone, Lewy et al (1989)
 - » Screening for DTA

7-minute screening

- Solomon, Hirschhoff, Kelly et al (1998)

7 Minute Screen

Cognitive components of the tasks

■ Enhanced Cued Recall

- Memory: visual-("object")-semantic & verbal



■ Category Fluency

- Verbal fluency: semantic category (animals)



■ Benton Temporal Orientation Test

- Orientation in time



■ Clock Drawing

- Visuoconstruction: Visual imagery-Constructional praxis



MMSE

- Werner, Heinick, Lin et al (1999)
 - » Repetition
- Leopold, Borson (1997)
 - » Alphabetical “world”
- Monsch, Foldi, Ermini-Funfschiling et al (1995)
 - » Improving the diagnostic accuracy
- Wells, Keyl, Chase et al (1992)
 - » Reduced set of items

Memory

- Buschke, Kulansky, Katz et al (1999)
 - » Memory impairment screen
- O'Carroll, Conway, Rynan et al (1997)
 - » Delayed word recall (Alzheimer vs Depression)
- Coen, Kirby, Swanwick et al (1997)
 - » Delayed word recall test (depression vs mild DTA)
- Soinien, Scheltens (1998)
 - » Early diagnostic indices of DTA

Comparisons

- Van Gorp, Marcotte, Sultzer et al (1999)
 - » MMSE vs. MDRS: adjusting for age and schooling
- Burkart, Heum, Maier et al (1998)
 - » SIDAM, ADAS, MMSE

Combinations

- Tierney, Szalay, Snow et al (1996)
 - » Proposal: Rey-OCF (delayed) & WMS mental control
- Cahn, Salmon, Butters et al (1995)
 - » Differences between community and clinical samples
- Devanand, Folz, Gorlyn et al (1999)
 - » Prediction: (modified) MMSE, Selective reminding test, Verbal fluence, block design

Neuropsychology- Neuroimaging

- Muller, Moller, Stippel et al (1999)
 - » SPECT/MMSE
- Wisser, Scheltens, Verhey et al (1999)
 - » RM/CAMCOG
- Zakzanis (1998)
 - » Tests: CVLT, WMS-R (sensitivity); Images: specificity

Conclusions I

- Standardization: Cross-cultural adaptation guidelines
- **The review: The majority of papers show important methodological limitations**
- Good/excellent paper: Buschke, Kulansky et al. Screening of dementia with the memory impairment screen. *Neurology*, 1999; 52:231-238

Conclusions II

- Importance of age and education adjustment: better classification accuracy
- Guideline: Delayed recall memory tests are recommended for the early diagnosis of AD

EBM

TESTS AND PROTOCOLS

Recommended neuropsychological test battery... REASONS

- Most sensitive to support a diagnosis?
- Theoretical speculation?
- Clinical experience?
- Clinical lore¹?
- Subjective appraisal of the published literature?

**TEST BATTERY WITH EMPIRICALLY
DERIVED TEST INCLUSION SENSITIVITIES**

$p < 0.05$ versus d

- p = significación
- d = tamaño del efecto (size effect)

Effect size estimate d

$p < .05$ (dichotomuos = “statistically significant”): What is the magnitude of effect?

$$\frac{\text{Patient mean} - \text{control mean}}{\text{pooled standard deviation}} = d \longrightarrow \text{Overlap percent (OL\%)}$$

Complete discriminability
between
experimental and control groups

$$d > 3.0 \text{ OL\%} < 5$$

0.00	→	100.0
0.8	→	52.6
1.0	→	44.6
1.5	→	29.3
2.0	→	18.9
2.6	→	10.7
2.8	→	8.8
3.0	→	7.2
3.2	→	5.8
4.0	→	2.3

EBM: Example 2

Selection of neuropsychological tests

Recommended neuropsychological test battery... REASONS

- Most sensitive to support a diagnosis?
- Theoretical speculation?
- Clinical experience?
- Clinical lore¹?
- Subjective appraisal of the published literature?

**TEST BATTERY WITH EMPIRICALLY
DERIVED TEST INCLUSION SENSITIVITIES**

DTA: SELECTION OF TESTS (Moss, Albert y Kemper, 1992), I

■ ATTENTION

- Auditory Continuous Performance Test
- Letter cancellation

■ EXECUTIVE FUNCTION

- Trail Making Test (TMT)
- Proverb Interpretation
- Wisconsin Card Sorting Test (WCST)
- Similarities subtest, WAIS-R

■ LANGUAGE

- Boston Naming Test (BNT), BDAB, writing sample
- Halstead-Wepman Aphasia Screening Test
- Wide Range Achievement Test-Revised
- Controlled Word Association Test

DTA: SELECTION OF TESTS (Moss, Albert y Kemper, 1992), II

■ VISUOSPATIAL-VISUOMOTOR

- Figure copying
- Finger tapping

■ MEMORY

- Wechsler Memory Scale - Revised
- Delayed Recognition Span Test (DRST)
- California Verbal Learning Test (CVLT)
- Rey Auditory Verbal Learning Test (RAVLT)

■ BEHAVIOR, PERSONALITY

- Profile of Mood State
- Visual Analog Depression Scale

Measurement standards for individual patient use

(Peña-Casanova, Int Psychogeriatrics, 9:105-114, 1997)

- 1.- Practicality
- 2.- Extent of neuropsychological measures
- 3.- Depth of measurement
- 4.- Cross-sectional measurement precision
- 5.- Longitudinal measurement (monitoring) precision
- 6.- Validity
- 7.- Standardization

Measurement standards for individual patient use (Peña-Casanova, Int Psychogeriatrics, 9:105-114, 1997)

3.- Depth of measurement

- Minimal floor and ceiling effect

4.- Cross-sectional measurement precision

- Small standard errors of measurement.
- Internal consistency

5.- Longitudinal measurement (monitoring) precision

- Test-retest reliability (>.90)

6.- Validity

- Construct: convergent and discriminant validity
- Validity for individual patient applications: screening & diagnosis (sensitivity & specificity)
- Sensitivity to longitudinal change

7.- Standardization

- Uniform administration and scoring procedures

Neuropsychometric Issues

- **Reliability: stability of an assessment instrument**
 - Reliability coefficient
 - Intra-judge reliability, Inter-judge (rater) reliability
 - Parallel-form reliability
 - Test-retest reliability
 - Split-half reliability
- **Validity: the extent to which a test measures the factor is intended to measure (test's usefulness)**
 - (Content validity. Construct validity)
 - Discriminant validity. Convergent validity
 - Predictive validity. Ecological validity
- **Factor analysis: the identification underlying variables in a large set of measures**

Effect size estimate d

$p < .05$ (dichotomuos = “statistically significant”): What is the magnitude of effect?

$$\frac{\text{Patient mean} - \text{control mean}}{\text{pooled standard deviation}} = d \longrightarrow \text{Overlap percent (OL\%)}$$

Complete discriminability
between
experimental and control groups

$d > 3.0$ OL% < 5

0.00	→	100.0
0.8	→	52.6
1.0	→	44.6
1.5	→	29.3
2.0	→	18.9
2.6	→	10.7
2.8	→	8.8
3.0	→	7.2
3.2	→	5.8
4.0	→	2.3

AD: The review (Zakzanis, Leach & Kaplan, 1999)

- 199 studies published between 1984 and 1997
- 7,156 patients with DAT
- 8,772 normal healthy controls

<i>Variables</i>	<i>M</i>	<i>SD</i>	<i>Range</i>	<i>N</i>
<i>DAT samples</i>	36	41	6-354	199
<i>Control samples</i>	44	91	5-990	199
<i>Patient's age</i>	71.6	4.4	61.7-86.9	192
<i>Duration of illness (yrs)</i>	3.6	1.4	0.6-7.0	44
<i>Percentage of males</i>	45.6	16.8	0.0-100	134
<i>Patient's education</i>	12.5	2.3	5.1-18.0	162

DAT: Effect size by test results in rank order

Zakzanis, Leach & Kaplan, 1999.

<i>Neuropsychological test/ variable</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>Min.</i>	<i>Max.</i>	<i>Nfs</i>
	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	
<i>WMS-R Mem Quotient</i>	7	-4.64	1.26	-3.16	-6.16	3241
<i>Buschke SRT del recall</i>	4	-4.63	2.39	-1.99	-7.41	1848
<i>CVLT long del free rec</i>	4	-4.47	1.59	-3.02	-6.72	1784
<i>CVLT long del cued rec</i>	3	-4.02	0.42	-3.54	-4.30	1203
<i>CVLT short del free rec</i>	4	-3.90	0.43	-3.35	-4.38	1556
<i>Mattis DRS mem scale</i>	10	-3.77	0.89	-2.58	-5.05	3760
<i>Rey-OCF delayed recall</i>	7	-3.74	0.93	-2.95	-5.70	2611

DAT: Effect size by test results in rank order

Zakzanis, Leach & Kaplan, 1999.

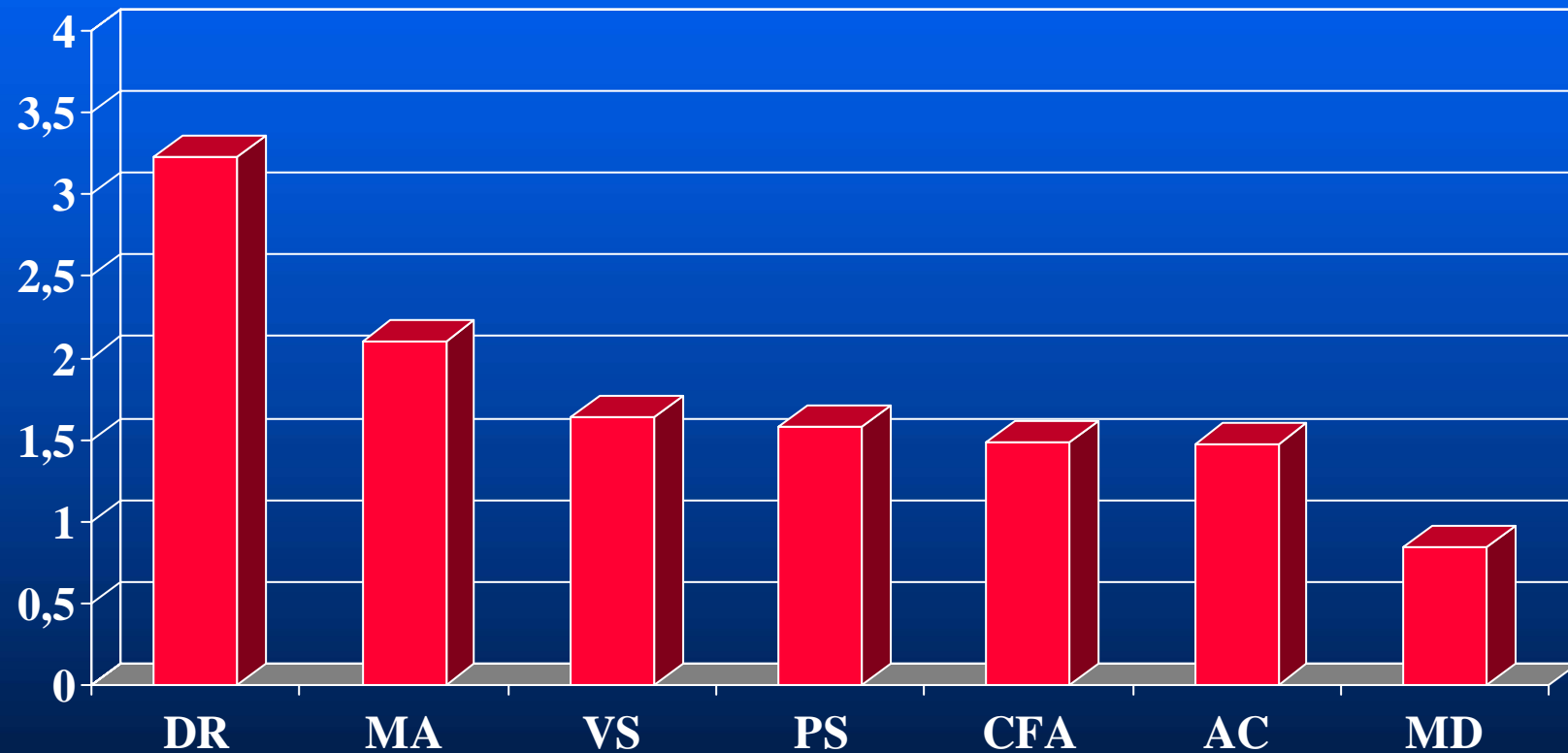
-4.64	WMS-R memory quotient	-3.11	Mattis DRS total score	
-4.63	Buschke SRT delayed recall	-3.01	WMS-R Visual reprod. II del r	
-4.47	CVLT long delay free recall	-3.00	CVLT recognition	7,2%OL
-4.02	CVLT long delay cued recall	-2.94	CVLT list A trial 5	
-3.90	CVLT short delay free recall	2.74	CVLT false recognition	
-3.77	Mattis DRS memory scale	-2.73	MMSE	10%OL
-3.74	ROCF delayed recall	-2.66	CVLT list B	
-3.47	CVLT short delay cued recall	-2.64	ROCF immediate reprod.	
-3.40	CVLT total recall trials 1-5	-2.60	RAVLT trial 1	
-3.36	WMS-R logical memory II dr	-2.60	WMS-R log. mem. I imm recall	
-3.31	RAVLT delayed recall	-2.47	Semantic fluency	15%OL
-3.11	Buschke SRT total recall	-2.39	WAIS-R Arithmetic	

DAT: Effect sizes by neuropsychological domain

Zakzanis, Leach & Kaplan, 1999.

<i>Function</i>	<i>Mean d</i>	<i>SD d</i>	<i>N</i>	<i>Min. d</i>	<i>Max.d</i>
<i>Delayed Recall</i>	3.23	1.46	74	0.42	7.72
<i>Memory acquisition</i>	2.10	1.19	189	0.00	5.16
<i>Verbal skill</i>	1.64	0.93	149	0.00	4.66
<i>Performance skill</i>	1.58	1.04	107	0.00	6.29
<i>Cog. Flexibility/Abst</i>	1.49	0.77	122	0.07	3.42
<i>Attention/conc</i>	1.47	1.00	69	0.15	6.32
<i>Manual dexterity</i>	0.85	0.36	8	0.53	1.38

Dementia of the Alzheimer's Type: Effect sizes by neuropsychological domain



DR: delayed recall; MA: memory acquisition; VS: verbal skills; PS: performance skills
CFA: cognitive flexibility-abstraction; AC: Attention/concentration; MD: manual dexterity

FTD: The review (Zakzanis, Leach & Kaplan, 1999)

- 8 studies published between 1985 and 1997
- 88 patients with FTD
- 100 normal healthy controls

<i>Variables</i>	<i>M</i>	<i>SD</i>	<i>Range</i>	<i>N</i>
<i>FTD samples</i>	11	3.5	7-16	8
<i>Control samples</i>	12.5	8.1	6-31	8
<i>Patient's age</i>	64.3	1.8	63-68	8
<i>Duration of illness (yrs)</i>	3.3	1.1	1.8-4.8	6
<i>Percentage of males</i>	48.5	12.8	37-71	6
<i>Patient's education (yrs)</i>	11.9	3.9	6.6-17	8

FTD: Effect size by test results in rank order

Zakzanis, Leach & Kaplan, 1999.

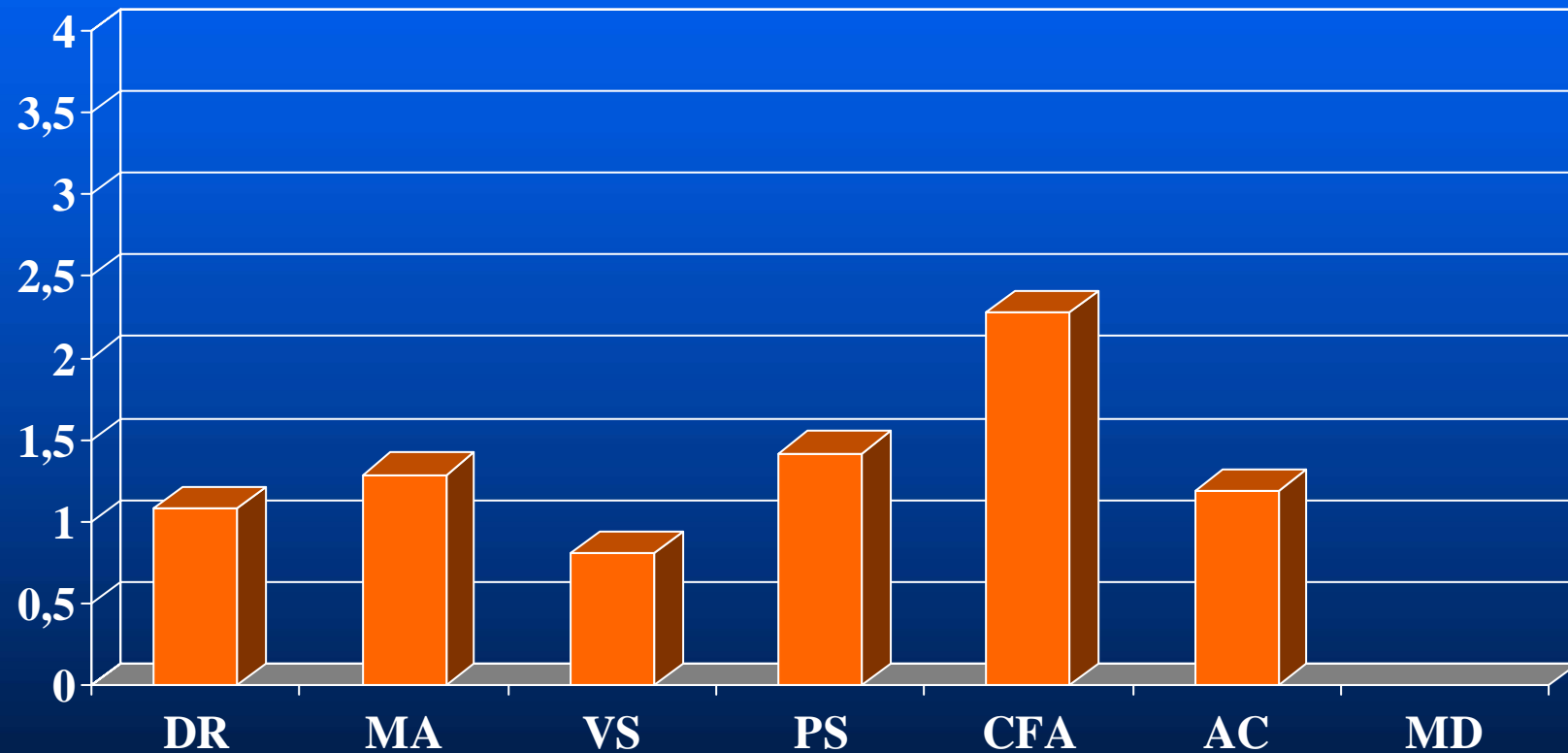
<i>Neuropsychological test/ variable</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>Min.</i>	<i>Max.</i>	<i>Nfs</i>
	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	
<i>Semantic fluency</i>	1	-4.14	-	-4.14	-4.14	413
<i>WCST-categories achiev.</i>	3	-3.28	2.58	-1.14	-6.14	981
<i>MMSE</i>	6	-3.14	1.33	-2.34	-5.78	1878
<i>WAIS-R Perform. IQ</i>	1	-2.52	-	-2.52	-2.52	251
<i>WAIS-R Block Design</i>	1	-2.45	-	-2.45	-2.45	244
<i>WCST-perseverations</i>	3	-2.30	0.82	1.26	2.74	687
<i>COWAT</i>	5	-2.29	0.94	-1.16	-3.57	1140

FTD: Effect sizes by neuropsychological domain

Zakzanis, Leach & Kaplan, 1999.

<i>Function</i>	<i>Mean d</i>	<i>SD d</i>	<i>N</i>	<i>Min. d</i>	<i>Max.d</i>
<i>Cog. Flexibility/Abst</i>	2.28	0.98	12	1.16	4.14
<i>Performance skill</i>	1.42	0.91	6	0.36	2.52
<i>Memory adqu.</i>	1.29	0.83	14	0.13	2.50
<i>Attention/conc</i>	1.19	0.57	4	0.44	1.81
<i>Delayed recall</i>	1.08	0.78	10	0.18	2.95
<i>Verbal skill</i>	0.81	0.39	6	0.42	1.44
<i>Manual dexterity</i>	-	-	-	-	-

Fronto-Temporal-Dementia: Effect sizes by neuropsychological domain



DR: delayed recall; MA: memory acquisition; VS: verbal skills; PS: performance skills
CFA: cognitive flexibility-abstraction; AC: Attention/concentration; MD: manual dexterity

PPA: The review (Zakzanis, Leach & Kaplan, 1999)

- 22 studies published between 1982 and 1997
- 55 patients with PPA
- 162 normal healthy controls

<i>Variables</i>	<i>M</i>	<i>SD</i>	<i>Range</i>	<i>N</i>
<i>PPA samples</i>	3.0	2.5	1-10	22
<i>Control samples</i>	40	42	10-99	4
<i>Patient's age</i>	62	5.6	51-73	22
<i>Duration of illness (yrs)</i>	8.1	2.9	4-12	13
<i>Percentage of males</i>	75	33	0-100	22
<i>Patient's education (yrs)</i>	12.2	5.8	6-20	4

PPA: Effect size results in rank order

Zakzanis, Leach & Kaplan, 1999.

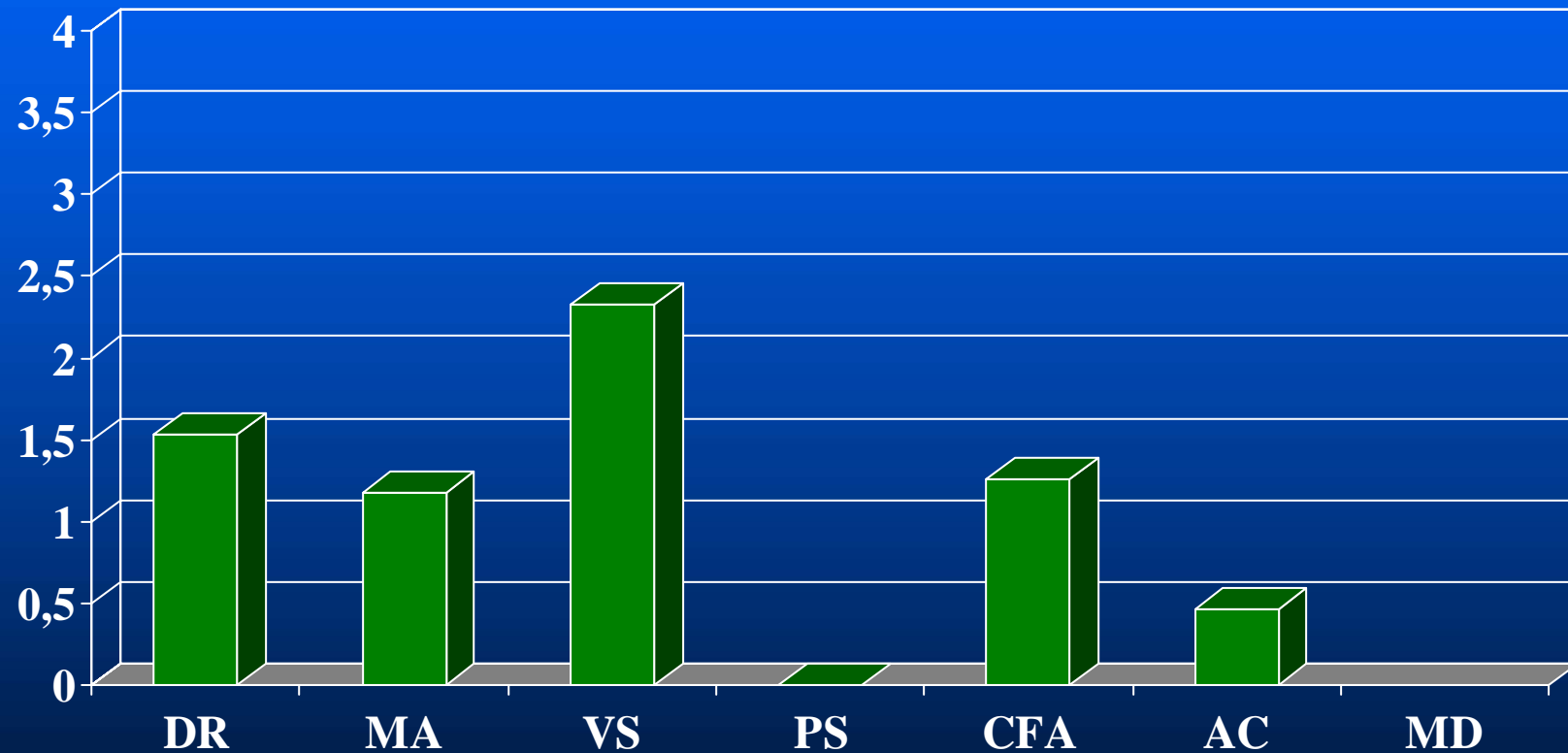
<i>Neuropsychological test/ variable</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>Min.</i>	<i>Max.</i>	<i>Nfs</i>
	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	
<i>Boston Naming Test</i>	8	-6.06	2.87	-1.30	-10.7	4840
<i>RAVLT delayed recall</i>	3	-4.42	1.00	-3.27	-5.00	1323
<i>Mattis DRS Total score</i>	1	-3.74	-	-3.74	-3.74	373
<i>MMSE</i>	2	-3.25	1.06	-2.50	-4.00	650
<i>Mattis DRS init/persev s</i>	1	-3.13	-	-3.13	-3.1	3312
<i>RAVLT trial 5</i>	2	-3.09	1.07	-2.33	-3.85	616
<i>WMS-R paired associat.</i>	1	-2.12	-	-2.12	-2.12	211

PPA: Effect sizes by neuropsychological domain

Zakzanis, Leach & Kaplan, 1999.

<i>Function</i>	<i>Mean d</i>	<i>SD d</i>	<i>N</i>	<i>Min. d</i>	<i>Max.d</i>
<i>Verbal skill</i>	2.33	2.77	33	0.67	-10.69
<i>Delayed recall</i>	1.53	2.62	10	2.92	-5.00
<i>Cog. Flexibility/Abst</i>	1.26	1.12	17	0.60	-3.13
<i>Memory adqu.</i>	1.18	1.44	27	2.53	-3.85
<i>Attention/conc</i>	0.47	1.20	7	1.26	-2.00
<i>Performance skill</i>	0.01	0.95	3	2.33	-2.33
<i>Manual dexterity</i>	-	-	-	-	-

Primary Progressive Aphasia: Effect sizes by neuropsychological domain



DR: delayed recall; MA: memory acquisition; VS: verbal skills; PS: performance skills
CFA: cognitive flexibility-abstraction; AC: Attention/concentration; MD: manual dexterity

PSP: The review (Zakzanis, Leach & Kaplan, 1999)

- 23 studies published between 1987 and 1997
- 229 patients with PSP
- 357 normal healthy controls

<i>Variables</i>	<i>M</i>	<i>SD</i>	<i>Range</i>	<i>N</i>
<i>PSP samples</i>	10	5.4	3-25	23
<i>Control samples</i>	17	16.7	4-82	23
<i>Patient's age</i>	66.4	5.4	55-85	23
<i>Duration of illness (yrs)</i>	3.8	0.9	2.1-4.9	13
<i>Percentage of males</i>	54.6	13.3	44-88	9
<i>Patient's education (yrs)</i>	11.1	2.9	8.5-15.3	10

PSP: Effect size results in rank order

Zakzanis, Leach & Kaplan, 1999.

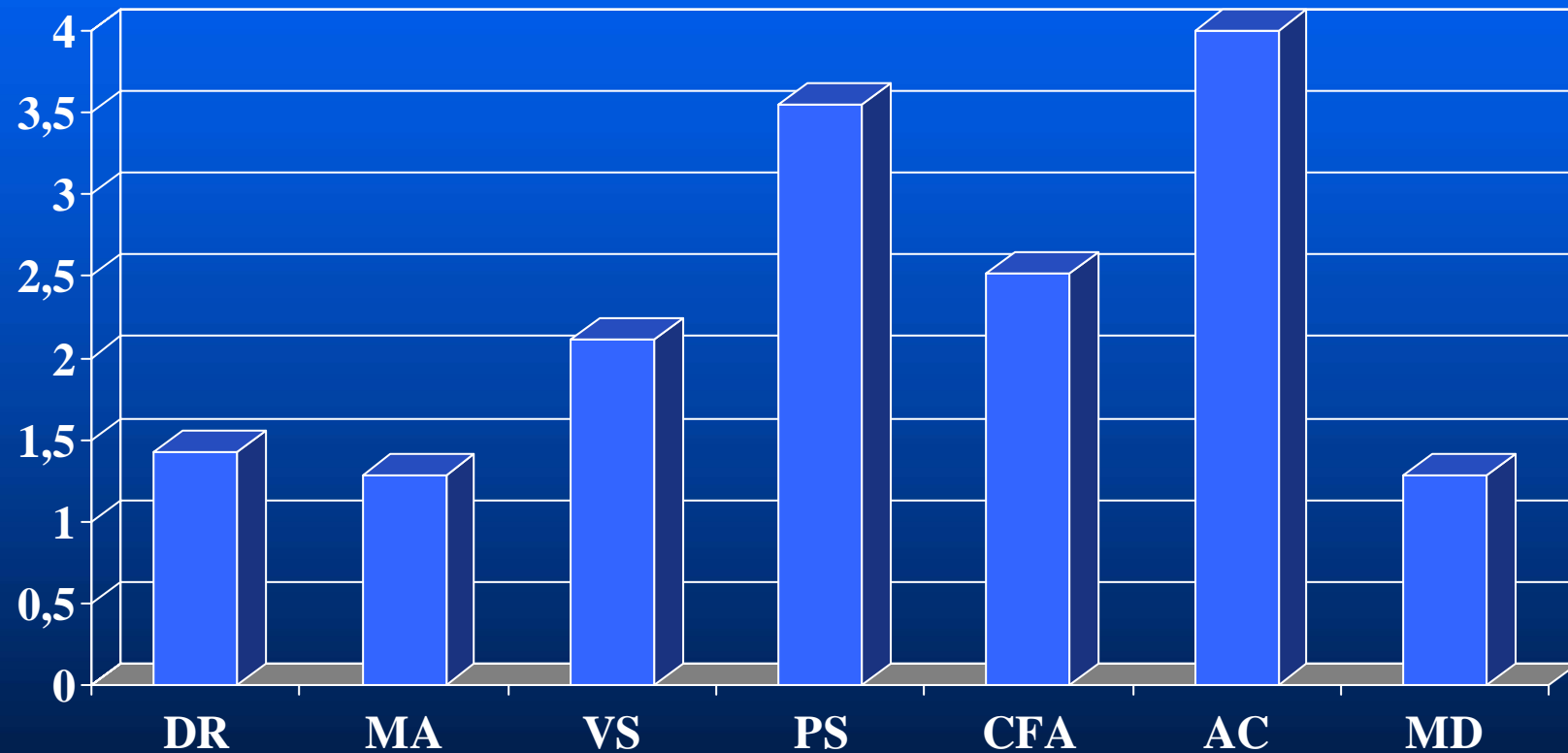
<i>Neuropsychological test/ variable</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>Min.</i>	<i>Max.</i>	<i>Nfs</i>
	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	
<i>Stroop word reading</i>	1	-4.46	-	-4.46	-4.46	445
<i>Mattis DRS Total Score</i>	1	-4.25	-	-4.25	-4.25	424
<i>Stroop color reading</i>	1	-4.12	-	-4.12	-4.12	411
<i>WAIS-R Full Scale IQ</i>	2	-3.60	0.39	-3.32	-3.87	718
<i>WAIS-R Perform. IQ</i>	2	-3.54	0.74	-3.02	-4.07	706
<i>TMT part A</i>	1	3.41	-	3.41	3.41	340
<i>Purdue Pegboard bilat</i>	2	-3.32	0.98	-4.01	-4.08	662

PSP: Effect sizes by neuropsychological domain

Zakzanis, Leach & Kaplan, 1999.

<i>Function</i>	<i>Mean d</i>	<i>SD d</i>	<i>N</i>	<i>Min. d</i>	<i>Max.d</i>
<i>Attention/conc</i>	4.00	0.54	3	3.41	4.46
<i>Performance skill</i>	3.54	0.74	2	3.02	4.07
<i>Manual dexterity</i>	2.73	1.06	7	1.28	4.01
<i>Cog. Flexibility/Abst</i>	2.52	1.26	19	1.18	5.75
<i>Verbal skill</i>	2.11	1.01	0	0.43	3.85
<i>Delayed recall</i>	1.43	0.51	3	1.12	2.02
<i>Memory adqu.</i>	1.28	0.86	7	0.09	2.77

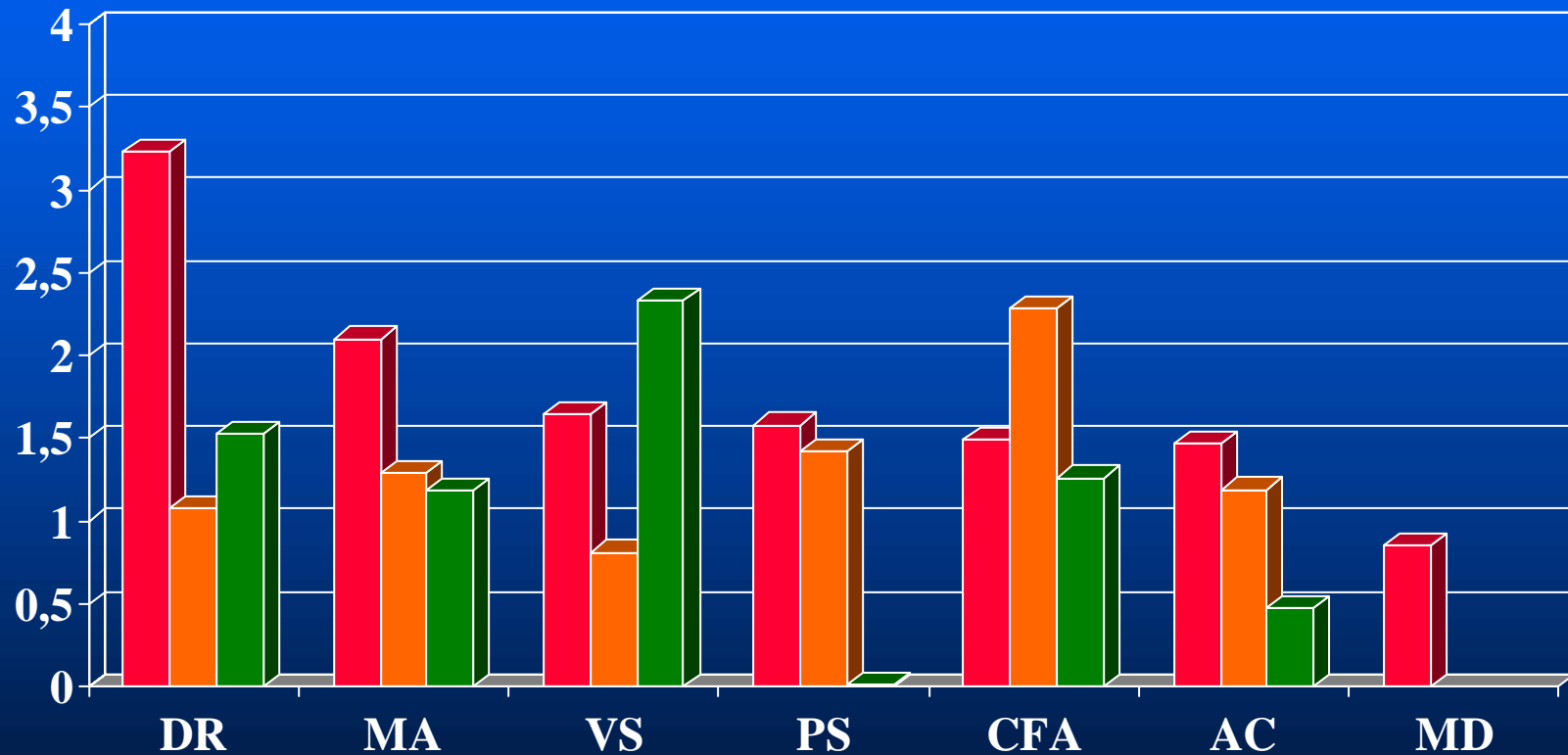
Progressive Supranuclear Palsy: Effect sizes by neuropsychological domain



DR: delayed recall; MA: memory acquisition; VS: verbal skills; PS: performance skills
CFA: cognitive flexibility-abstraction; AC: Attention/concentration; MD: manual dexterity

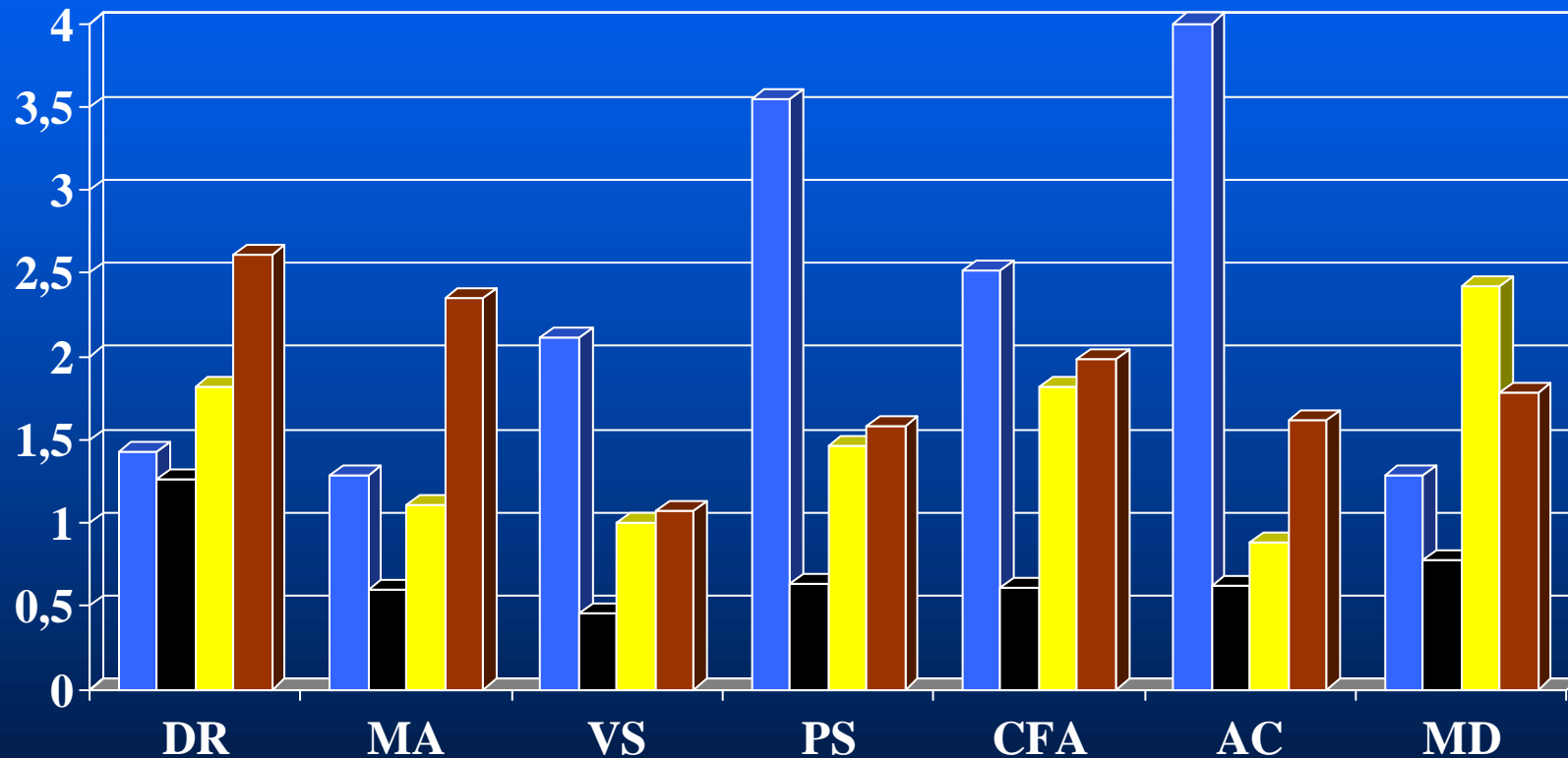
DAT, FTD, PPA:

Effect sizes by neuropsychological domain



PSP, PDnD, PDD, HD:

Effect sizes by neuropsychological domain



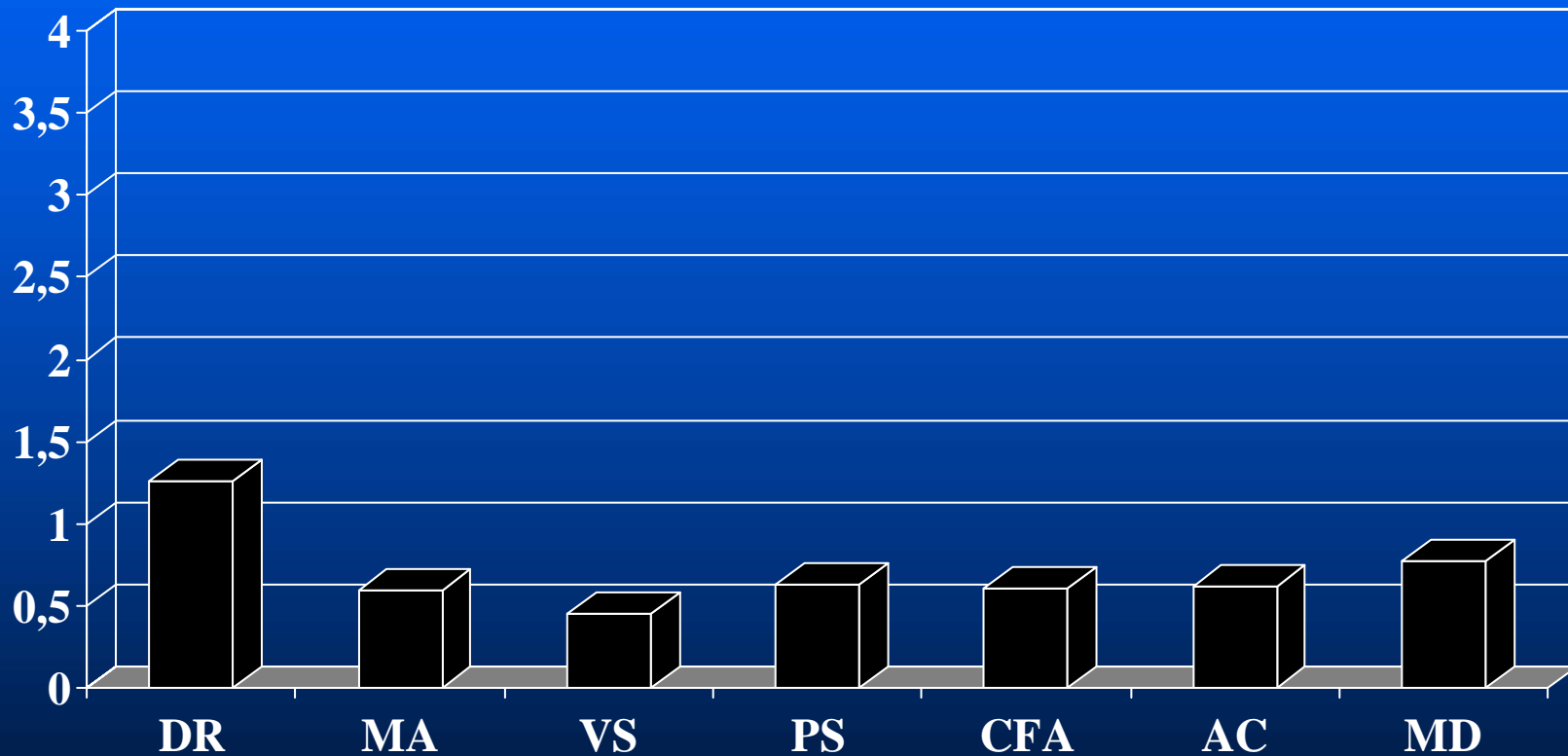
DR: delayed recall; MA: memory acquisition; VS: verbal skills; PS: performance skills
CFA: cognitive flexibility-abstraction; AC: Attention/concentration; MD: manual dexterity

PD-Nodem: The review (Zakzanis, Leach & Kaplan, 1999)

- 23 studies published between 1980 and 1997
- 2120 nondemented patient with PD
- 2464 normal healthy controls

<i>Variables</i>	<i>M</i>	<i>SD</i>	<i>Range</i>	<i>N</i>
<i>Nondem-PD samples</i>	29	20	8-107	75
<i>Control samples</i>	24	14	5-90	75
<i>Patient's age</i>	63	5.5	44-73	74
<i>Duration of illness (yrs)</i>	5.9	2.9	0.20-13	52
<i>Percentage of males</i>	61	9.4	44-80	45
<i>Patient's education (yrs)</i>	13.2	2.6	6.2-19	58

Parkinson's Disease - Nondemented: Effect sizes by neuropsychological domain

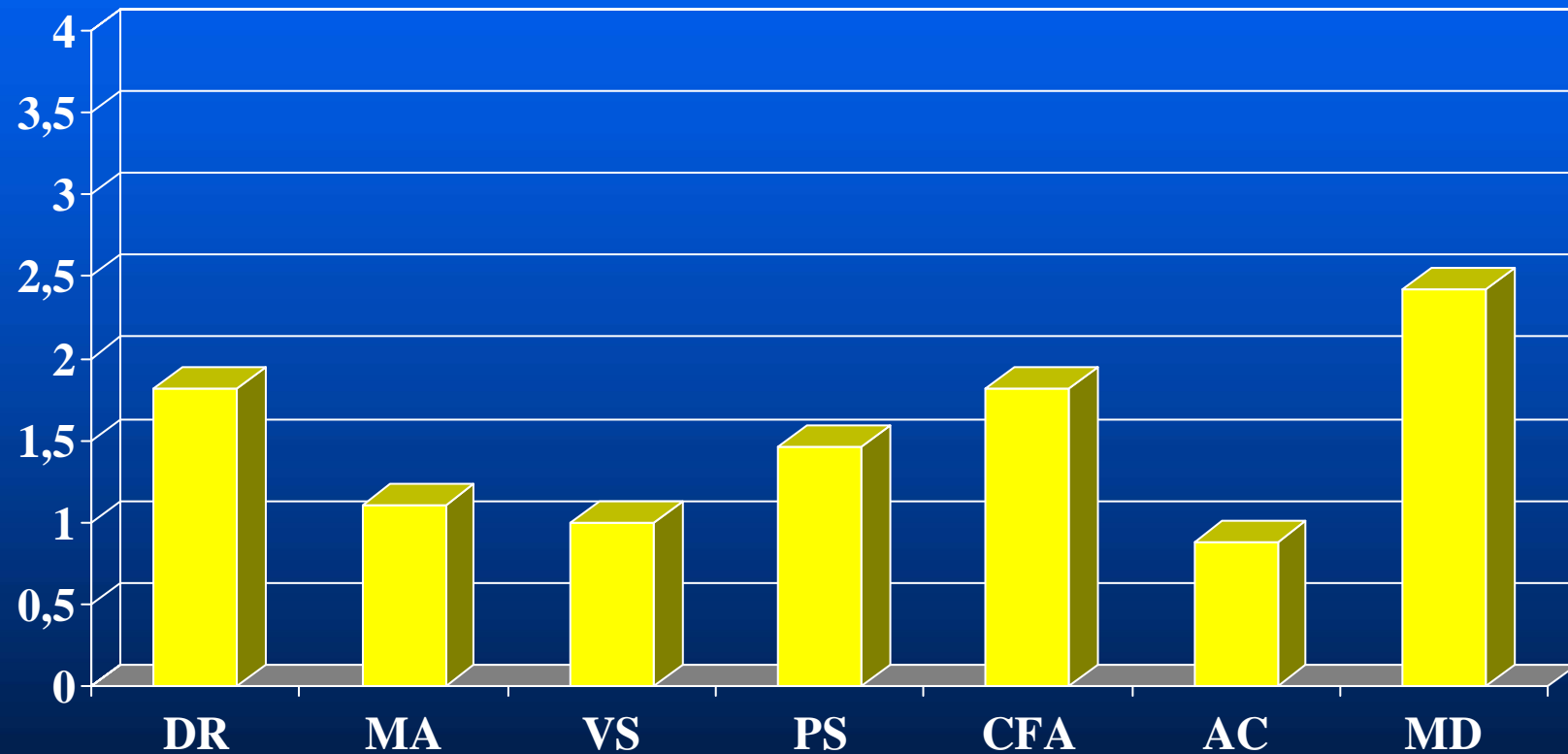


PD-dem: The review (Zakzanis, Leach & Kaplan, 1999)

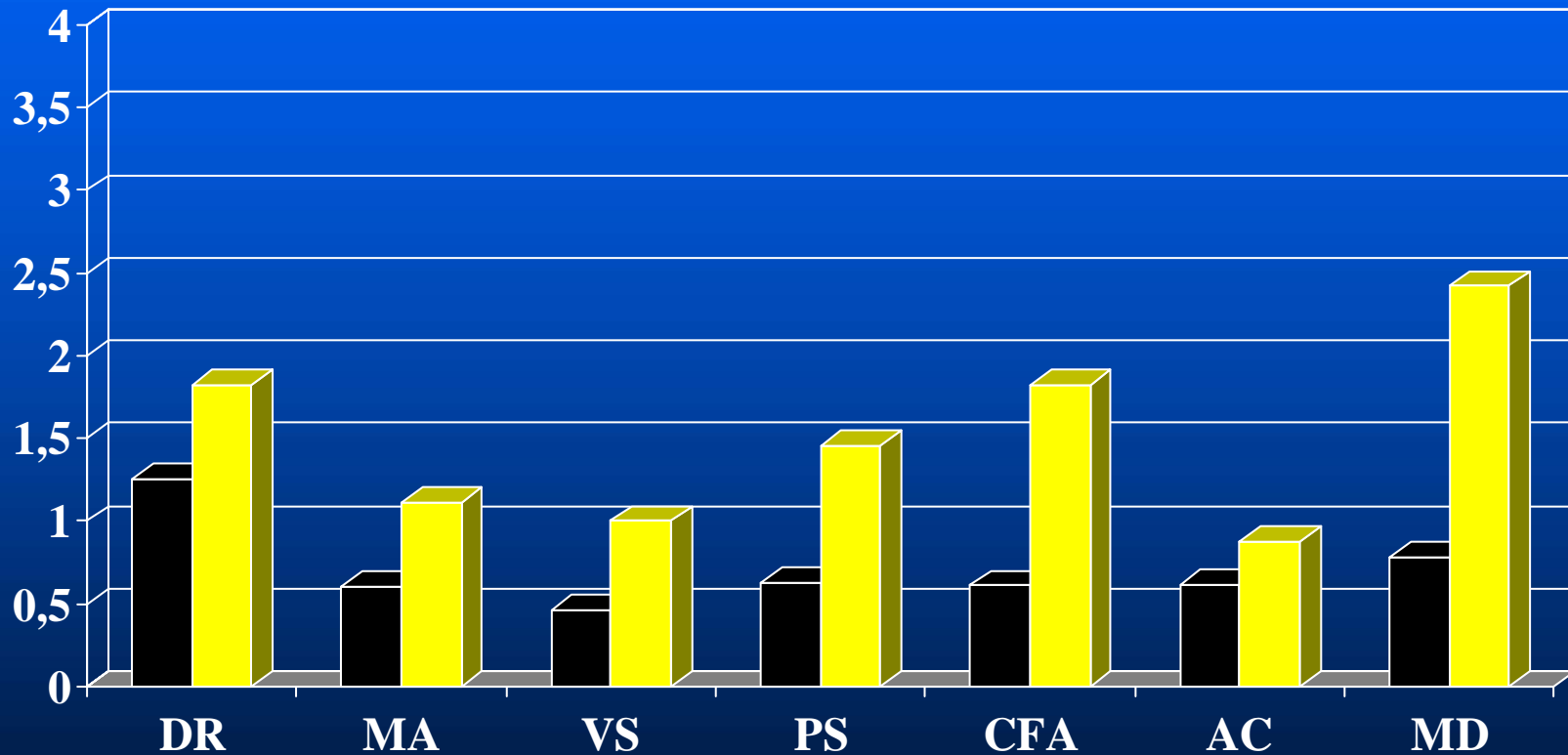
- 23 studies published between 1987 and 1997
- 588 demented patients with PD
- 2464 normal healthy controls

<i>Variables</i>	<i>M</i>	<i>SD</i>	<i>Range</i>	<i>N</i>
<i>Dem-PD samples</i>	26	21	5-76	24
<i>Control samples</i>	29	20	5-90	24
<i>Patient's age</i>	68	11	62-76	24
<i>Duration of illness (yrs)</i>	7.3	3.4	1.1-13	15
<i>Percentage of males</i>	68	17	38-100	13
<i>Patient's education (yrs)</i>	12.1	2.3	7-16	18

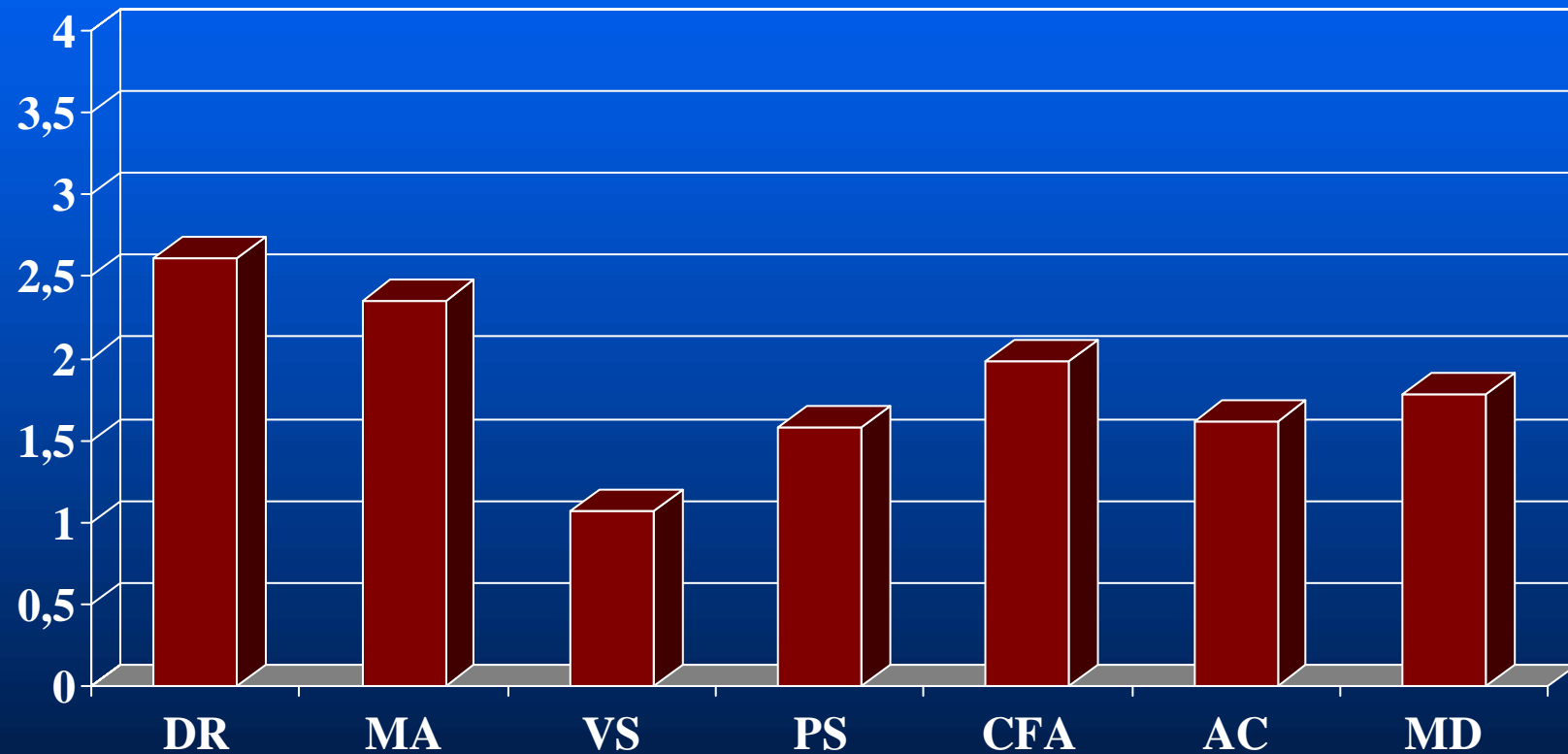
Parkinson's Disease - Demented: Effect sizes by neuropsychological domain



PD-Nondemented, PD-Demented: Effect sizes by neuropsychological domain

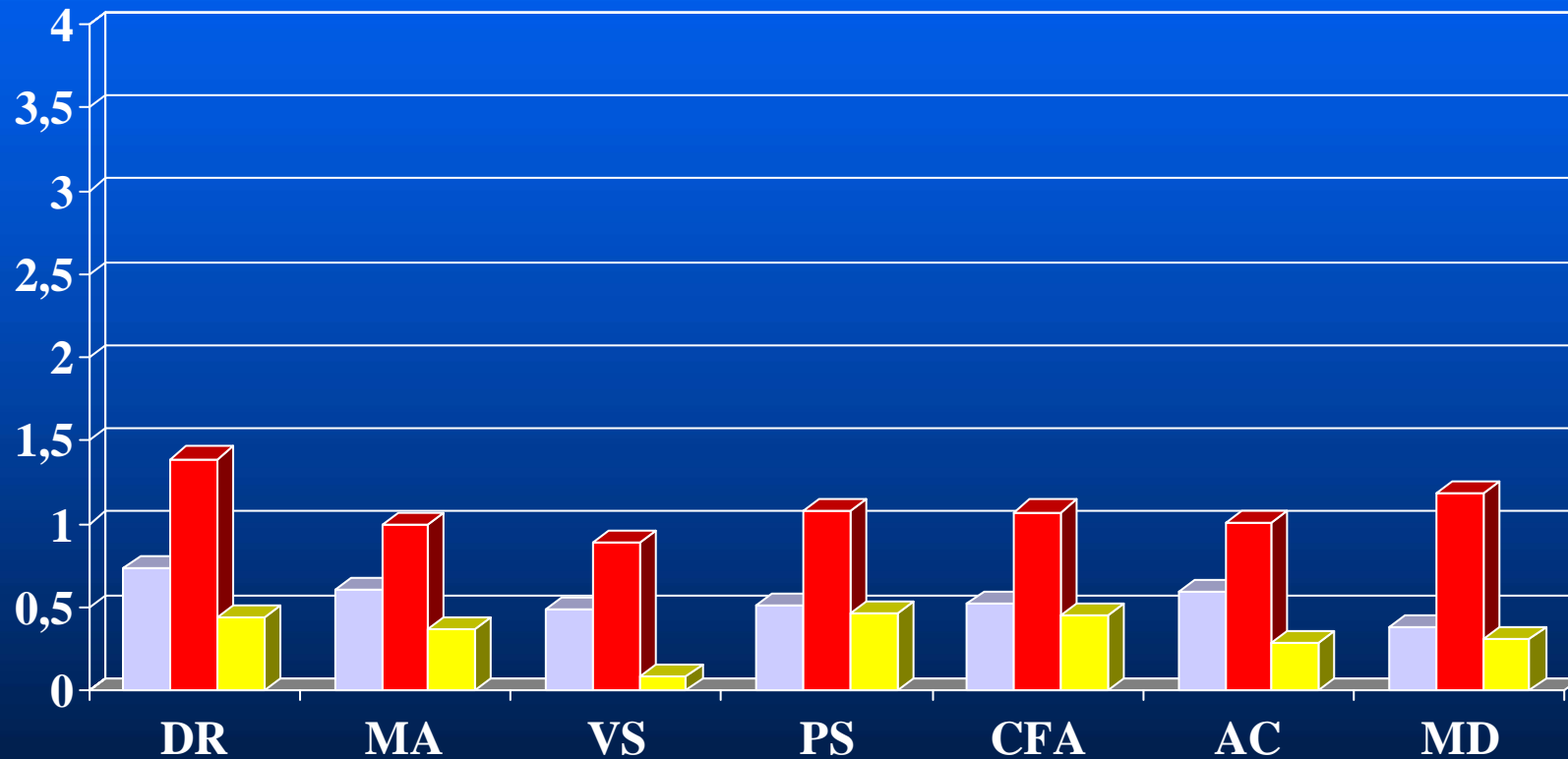


Huntington's Disease: Effect sizes by neuropsychological domain



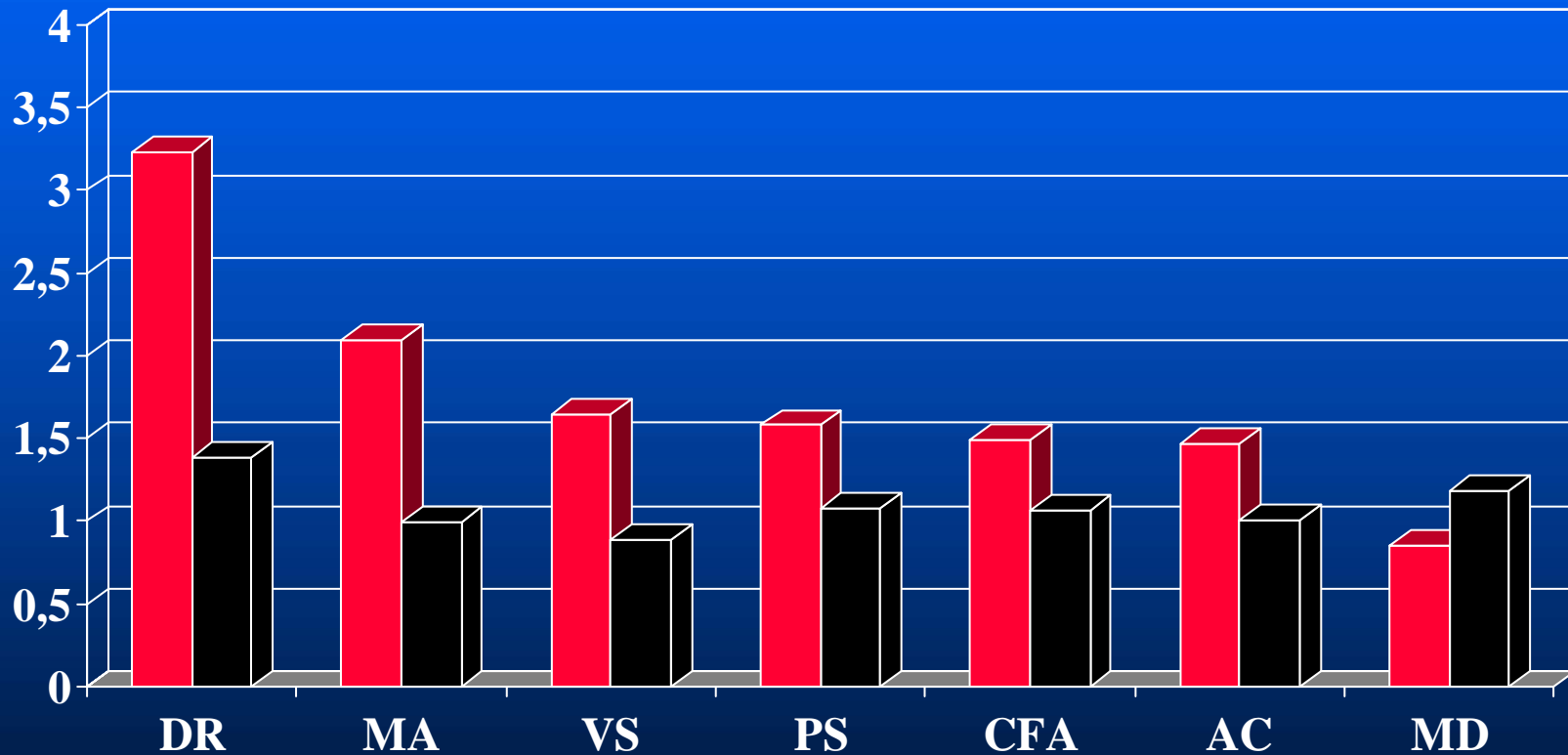
MDD, Sch, OCD:

Effect sizes by neuropsychological domain



DAT vs Sch:

Effect sizes by neuropsychological domain



Neuropsychological test battery, I

- Primary memory
 - WAIS-R digit span forwards
 - Consonant trigrams
- Working memory
 - WAIS-R digit span backwards
 - PASAT
 - WAIS-R arithmetic
- Semantic memory
 - WAIS-R information
 - WAIS-R vocabulary
 - NART
- Attention/Concentration
 - Stroop Color-word Interf. Test

Neuropsychological test battery, II

■ Visuoconstructional skills

- WAIS-R block design
- WAIS-R object assembly
- ROCF copy

■ Visuoperceptual abilities

- Facial recognition (Benton)
- Hooper Visual Organization T
- Judge of line orientation
- WAIS-R picture completion

■ Verbal skills

- COWAT
- Semantic fluency
- Boston Naming Test

■ Cognitive flexibility/abstract

- WAIS-R similarities
- WCST number of categories
- WCST perseverative responses

Neuropsychological test battery, III

■ Immediate memory

- CVLT trial 5 total
- RAVLT trial 5 total
- WMS-R logical memory I
- WMS-R visual reproduction I
- ROCF immediate reproduction

■ Delayed Memory

- CVLT Delayed Free Recall
- CVLT Delayed Cued Recall
- CVLT Delayed Recognition
- RAVLT Delayed Free Recall W
- RAVLT Delayed Recognition
- WMS-R logical memory II
- WMS-R Visual reproduction II

Neuropsychological test battery, IV

■ Complex Psychomotor Skills

- WAIS-R Digit Symbol
- Stroop Color Naming Test
- Stroop Word Reading Test

■ Simple Motor Skills

- Finger Tapping Test
- Grooved Pegboard Test
- Purdue Pegboard Test

■ Mood

- Beck depression inventory
- Hamilton Depression Rating Sc

■ Intellectual functioning

- WAIS-R Full IQ

Conclusions I

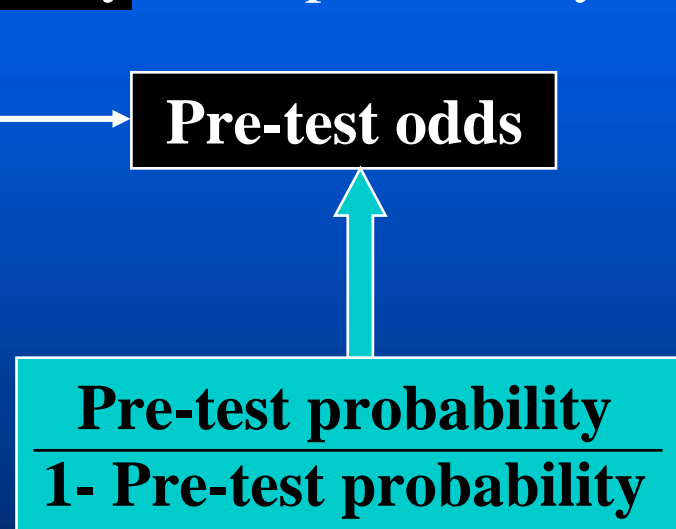
- Effect sizes versus p
- *The best battery*

EBM: Example 3

MEASUREMENT STANDARDS
AND LIKELIHOOD RATIOS

Operating Characteristics and Sampling: Toward useful validities

Operating characteristics take into account the prevalence of a disorder and the **a priori probability** that a patient may or may not have a disorder



Diagnostic test interpretation: The use of likelihood ratios

- A likelihood ratio for a *given diagnostic test result* give the *odds* that that test result comes from a person who has the disease for which the test was ordered.
- When the likelihood ratio is multiplied by the “pre-test” odds that the patient has the disease, the product is the “post-test” odds that the person has the disease.

PRE-TEST ODDS x LIKELIHOOD RATIO = POST-TEST ODDS


$$\frac{\text{Sensitivity}}{1-\text{Specificity}}$$

$$\text{Pre-test odds} = \frac{\text{Pre-test probability}}{1 - \text{Pre-test probability}}$$

(Prevalence: 0.15; 15%) = 0.18

<i>MMSE Score</i>	<i>Likelihood ratio</i>	<i>Post-test odds</i>	<i>Post-test Probability</i>	Prediction
24	11.15	1.98	0.6632	66.3%
23	17.73	3.13	0.7578	75.7%
22	32.44	5.73	0.8513	85.1%
21	41.22	7.27	0.8792	87.9%
20	114.52	20.21	0.9529	95.2%

(Adjusted)

$$\frac{\text{Sensitivity}}{1 - \text{Specificity}}$$

(0.18)

$$\frac{\text{Post-test odds}}{1 + \text{Post-test odds}}$$

$$\text{Pre-test odds} * \text{Likelihood ratio}$$

Likelihood ratio

- Greater than 10: large
- Between 5 and 10: moderate
- Between 2 and 4: small

Summary: Specificity > 90; LR >9.5

	<i>Cutting</i>	<i>Sens</i>	<i>Spec</i>	<i>LR</i>	<i>Pred. 15% rate</i>
<i>MMSE-Adj</i>	24	85.5	92.3	11.1	66.3
	23	78.3	97.5	17.7	75.7
<i>ADAS-Adj</i>	13	84.6	91.1	9.6	62.8
	14	83.7	93.5	12.9	69.5
<i>IDDD</i>	36	81.9	95.0	16.3	74.3
	37	80.1	95.5	18.1	76.2
<i>RDRS-2</i>	22	78.3	91.7	9.51	62.6
	23	69.3	95.2	14.7	72,2
<i>BDRS</i>	4	85.5	92.3	11.1	66.2
	4,5	81.9	94.4	14.6	72.0