

Differentiating Alzheimer’s Disease and Related Dementias Presenting with Isolated Mild Executive-Predominant Cognitive Impairment: Role of Neuropsychological Testing

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BACKGROUND:

Neurodegenerative disorders can present with isolated executive dysfunction at the mild cognitive impairment (MCI) stage. Early recognition and timely diagnosis of ADRD subtypes is important for patient counseling and initiation of appropriate treatment.

AIM:

To evaluate the utility of neuropsychological testing of patients with isolated dysexecutive MCI to differentiate between ADRD subtypes, Alzheimer’s Disease (AD), Lewy Body Dementia (DLB), Cerebrovascular Disease (CVD), and Frontotemporal Dementia (FTD) to improve early differential diagnosis.

METHODS

RESULTS

TABLES

DISCUSSION

REFERENCES

ACKNOWLEDGEMENTS

Secondary analysis of neuropsychological testing in the NACC database, clinical research data from 37 NIA-funded ADCs collected between 2005 and June 2024. One-way ANOVA was used, with a p-value <0.05 considered statistically significant

Inclusion Criteria

A. A primary diagnosis of non-amnesic mild cognitive impairment based on unified dataset (UDS) NACCTMCI code

B. Diagnosis of isolated executive dysfunction based on UDS NACCMCIE code

C. A primary clinical diagnosis of AD, DLB, CVD, or an FTD syndrome

D. CDR-Glob of 0.5 < CDR Glob < 1, and MMSE of 17 < MMSE < 29 or MOCA of 17 < MoCA < 26. Our final sample included HC participants with a CDR-Glob = 0 and CDR-SB = 0 and MMSE = 30 or a MoCA > 26

Exclusion Criteria

A. A significant pre-existing neurological condition other than a dementia subtype (eg. epilepsy, Parkinson’s disease)

B. Identified with moderate to severe mental illness; geriatric depression at or above 9 (GDS ≥ 9) or severe anxiety (Anxsev = 3)

C. A mixed pathology, such as a history of stroke or space occupying lesion

D. A dominantly inherited genetic mutation for AD (APP, PSEN-1, PSEN-2) or FTD (MAPT, PGRN, C9orf72, FUS, were excluded

Of 51, 836 participants available in data collected across the NACC database, 762 participants met our inclusion criteria for Isolated Mild Executive-Predominant Cognitive Impairment (n=762).

•FTD patients performed worse on Digit Span Backwards, phonemic and semantic fluency, and Benson Figure Delayed compared with AD and HC, and Benson figure copy compared with CVD and HC.

•DLB patients showed significantly poorer performance than AD, CVD, FTD, and HC on Trail Making Test B.

•AD patients exhibited the lowest score on Logical Memory IIA test and showed a trend toward lower scores compared with those with FTD.

•CVD patients showed the greatest impairment on the Boston naming task

Table 2: Baseline Cognitive Measures

Variable	HC (n=595)	AD (n=297)	DLB (n=182)	CVD (n=221)	FTD (n=62)	P value
MMSE	30.0 ± 0.2 ^{ns}	26.6 ± 2.2 ^{ab}	26.9 ± 1.8 ^{ab}	26.7 ± 1.9 ^{ab}	25.4 ± 3.1 ^{cd}	<.001
MoCA	29.0 ± 2.6 ^{ns}	22.3 ± 2.9 ^{ab}	22.6 ± 2.6 ^{ab}	21.9 ± 2.7 ^{ab}	21.5 ± 2.9 ^{ab}	<.001
CDR-SB	0 ± 0.1 ^{nsd}	1.9 ± 1.0 ^{ab}	2.0 ± 1.0 ^{ab}	1.7 ± 1.0 ^{ab}	2.2 ± 1.2 ^{ab}	<.001
C D R - G L O B	0 ± 0.02 ^{nsd}	0.5 ± 0 ^a	0.5 ± 0.04 ^a	0.5 ± 0.03 ^a	0.5 ± 0 ^a	<.001
N P I Q - t o t a l	1.9 ± 0.9 ^{nsd}	1.6 ± 0.8 ^{ab}	1.2 ± 0.5 ^{ab}	1.6 ± 0.8 ^{ab}	1.4 ± 0.7 ^{ab}	<.001
GDS	0.7 ± 1.3 ^{nsd}	2.7 ± 2.2 ^{ab}	3.4 ± 2.3 ^{ab}	2.9 ± 2.2 ^{ab}	4.1 ± 2.9 ^{cd}	<.001
N P I - Q A n x i e t y	1.4 ± 0.5	1.3 ± 0.5	1.4 ± 0.5	1.3 ± 0.5	1.5 ± 0.5	0.088

Table 3: Neuropsychological Measures by Domain

Variable	HC (n=595)	AD (n=297)	DLB (n=182)	CVD (n=221)	FTD (n=62)	P value
Executive Functioning						
Digit span backwards	5.3 ± 1.2 ^{nsd}	4.2 ± 1.2 ^{ab}	4.3 ± 1.1 ^{ab}	4.2 ± 1.1 ^{ab}	3.7 ± 1.3 ^{ab}	<.001
Trail Making Test Part B	72.5 ± 34.2 ^{nsd}	163.1 ± 81.5 ^{ab}	163.1 ± 76.4 ^{ab}	163.3 ± 78.3 ^{ab}	168.6 ± 90.5 ^{ab}	<.001
Memory						
Logical Memory IIA	13.9 ± 3.6 ^{nsd}	6.6 ± 4.4 ^{ab}	7.9 ± 4.3 ^{ab}	7.8 ± 4.6 ^{ab}	7.0 ± 4.4 ^{ab}	<.001
Benson Figure Copy Delayed	14.6 ± 3.6 ^{nsd}	9.0 ± 3.8 ^{ab}	8.4 ± 3.7 ^{ab}	8.2 ± 3.9 ^{ab}	8.0 ± 4.6 ^{ab}	<.001
Language						
Animals	22.4 ± 5.2 ^{nsd}	16.1 ± 4.9 ^{ab}	16.6 ± 4.9 ^{ab}	15.2 ± 4.8 ^{ab}	12.9 ± 5.5 ^{ab}	<.001
Boston Naming Test	28.2 ± 2.3 ^{nsd}	25.2 ± 4.2 ^{ab}	26.6 ± 3.6 ^{ab}	23.1 ± 6.1 ^{ab}	24.0 ± 6.9 ^{ab}	<.001
Correct L and F words	27.9 ± 10.1 ^{nsd}	22.7 ± 10.1 ^{ab}	22.6 ± 9.1 ^{ab}	21.8 ± 9.0 ^{ab}	14.7 ± 11 ^{ab}	<.001
Visuospatial						
Benson Figure Copy Test	16.4 ± 2.0 ^{nsd}	14.5 ± 2.0 ^{ab}	14.4 ± 2.3 ^{ab}	14.8 ± 1.8 ^{ab}	14.3 ± 2.8 ^{ab}	<.001

A. FTD patients exhibited impaired working memory and visuospatial function, likely related to underlying executive dysfunction. Reduced verbal fluency appeared primarily driven by impaired generative processes, with the overall pattern pointing to dorsolateral frontal dysfunction¹

B. DLB patients' performance patterns suggested deficits in cognitive flexibility, set-switching, and working memory reflecting the fluctuation in attention and prominent executive dysfunction associated with DLB⁴

C. AD patients demonstrated impaired verbal and visual memory, consistent with hippocampal involvement characteristic of AD³

D. CVD patients showed impaired naming performance was most consistent with deficits in word retrieval, likely reflecting disruption of subcortical circuit involvement²

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