Normative Study of the Russian TOMMORROW Neuropsychological Battery

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Introduction

Culturally sound neuropsychological metrics are required for global clinical trials that are designed to delay the progression of Alzheimer's disease (AD) from normal cognition to fully expressed disease. Few neuropsychological tests have been validated and normed for use with non-English-speaking populations.

The TOMMORROW Study is an international clinical trial that uses the National Institute on Aging–Alzheimer's Association (NIA-AA) 2011 criteria for mild cognitive impairment due to AD (MCI-AD) as the primary end point. The trial requires validation of a neuropsychological battery both to detect MCI-AD in each language and to evaluate cognitive decline and response to treatment.

To facilitate detection of subtle cognitive change in presymptomatic AD, we conducted a validation and normative study of the TOMMORROW neuropsychological battery in Tomsk, Russia.

Methods

Prior to the validation study, linguistic and cultural adaptation of the neuropsychological battery was completed in Russian. This was done in accordance with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines and included forward and back translation, cognitive debriefing interviews, and review by in-country experts and study lead neuropsychologists.

Sample

Cognitively Normal Controls

- Approximately n=50 in each of 4 age strata (65-69, 70-74, 75-79, 80-88).
- Each age strata required to have a pre-set minimum number of males and females and individuals with low and high education.
- Required to have Mini Mental State Examination (MMSE) scores >24 and complete clinical evaluation to confirm normal cognition.
- Mean (SD) MMSE score = 28.8 (1.19); range = 25-31; with age and education adjustment.

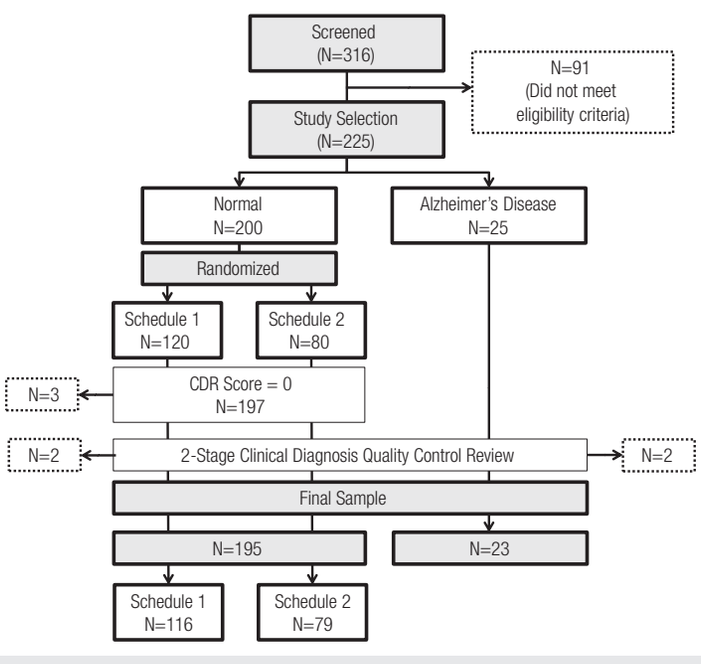
Individuals with AD

- N=25 with clinically diagnosed AD cases of dementia based on National Institute of Neurological Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria of mild to moderate dementia severity.
- Mean (SD) age = 74.8 (5.4); range 65-88.
- Mean (SD) MMSE score = 19.3 (3.84); range = 13-26; indicating mild to moderate dementia.

See **Figure 1** for sample characteristics and study design.

See CTAD posters (P1-49, P1-53, P-54, P1-69) and oral presentation (Welsh-Bohmer, Nov 6) for further details about study methods.

Figure 1. Study Design



Results

Reliability

- Test-retest reliability and Alternate form reliability were supported (see **Table 1**).

Table 1. Test-Retest and Alternate Form Reliability

Test	Test-Retest Reliability		Alternate Form Reliability	
	N	Pearson *r*	N	Pearson *r*
CVLT-II Short-Delay Free Recall [S]	116	0.791*	75	.647*
CVLT-II Long-Delay Free Recall [S]	116	0.762*	75	.616*
BVMT-R Delay Recall [S]	116	0.752*	74	.680*
Digit Span Forward	191	0.685*	—	—
Digit Span Backward	191	0.682*	—	—
Digit Span Total	191	0.799*	—	—
Trails A Total Seconds	191	0.779*	—	—
Trails B Total Seconds	191	0.696*	—	—
MINT Total	191	0.859*	—	—
Semantic Fluency	191	0.577*	—	—
Lexical Fluency: Total Words	191	0.809*	—	—
BVMT-R Copy [S]	116	0.621*	—	—
Clock Drawing Test	191	0.602*	—	—

Notes: [S] Standard forms for CVLT-II or Form 1 for BVMTR. Outlier correction was not accounted for in original analyses.
**P*<0.001.
BVMT-R: Brief Visuospatial Memory Test–Revised; CVLT-II: California Verbal Learning Test – second edition; MINT: Multilingual Naming Test.

Validity

- Criterion validity was supported (see **Tables 2 & 3** and **Figure 2**).
- Construct validity was supported: High correlations were observed among tests in related domains in healthy controls (*r* = .43-.87).

Table 2. Criterion Validity

Cognitive Test	Normal Controls Participants (n=195)	Diagnosed AD Participants (n=23)	F-Statistic[a]	Cohen's *d*[b]
CVLT-II Long-Delay Free Recall Correct	10.1 (0.19)	1.1 (0.55)	75.6	3.55
MINT	29.4 (0.20)	21.3 (0.57)	81.7	3.13
CVLT-II Short-Delay Free Recall Correct	9.5 (0.19)	1.9 (0.55)	57.2	3.01
BVMT-R Delayed Recall	8.3 (0.17)	1.8 (0.50)	73.3	2.86
Trails A Total Seconds	55.4 (2.21)	124.3 (6.29)	34.5	2.40
Trails B Total Seconds	155.9 (3.88)	274.2 (11.83)	39.8	2.35
Clock Drawing Test	8.5 (0.11)	6.0 (0.33)	27.6	1.74
Semantic Fluency (animals)	19.5 (0.39)	11.0 (1.10)	25.8	1.69
Lexical Fluency: Total Words	31.0 (0.72)	18.8 (2.04)	24.3	1.31
BVMT-R Copy Accuracy	11.3 (0.08)	10.1 (0.24)	23.0	1.10
Digit Span Backward	5.8 (0.13)	4.0 (0.38)	13.0	1.06
Digit Span Total	14.7 (0.22)	12.1 (0.64)	12.1	0.89
Digit Span Forward	8.9 (0.13)	8.1 (0.38)	6.0	0.45

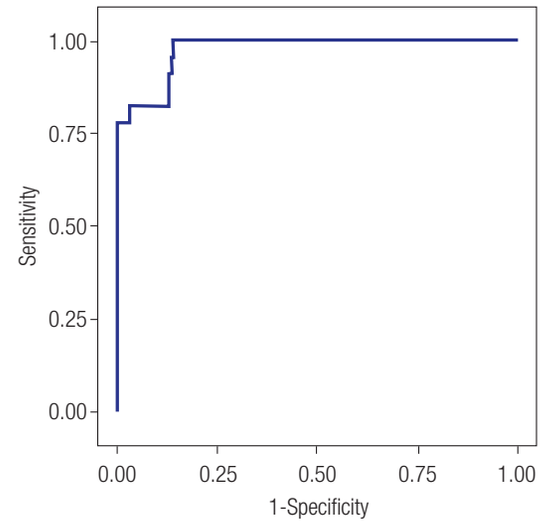
BVMT-R: Brief Visuospatial Memory Test–Revised; CVLT-II: California Verbal Learning Test – second edition; MINT: Multilingual Naming Test.

Table 3. Discrimination of AD Cases From Normal Controls

Model	Sensitivity	Pos Pred Value	Specificity	Neg Pred Value	Total Pseudo R^2	Partial Pseudo R^2		
						Age	Sex	Education
CVLT-II Short-Delay Free Recall	91.3	70.0	95.4	98.9	0.36	—	—	—
CVLT-II Short-Delay Free Recall w/Covariates	91.3	91.3	99.0	99.0	0.40	0.01*	0.02*	ns
CVLT-II Long-Delay Free Recall	91.3	84.0	97.9	99.0	0.39	—	—	—
CVLT-II Long-Delay Free Recall w/Covariates	91.3	91.3	99.0	99.0	0.43	ns	0.02*	ns
Composite Score	78.3	78.3	97.4	97.4	0.36	—	—	—
Composite Score w/Covariates	82.6	82.6	97.9	97.9	0.41	0.02*	ns	ns

**P*<0.05.
CVLT-II: California Verbal Learning Test – second edition; ns: not significant.

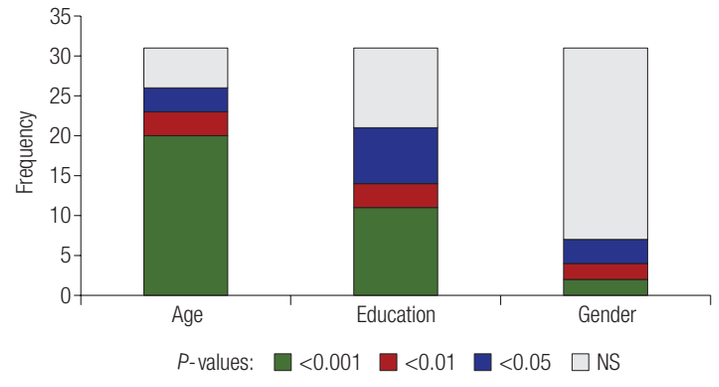
Figure 2. Receiver Operator Characteristics Curves for Composite Scores (Without Covariates)



Norms

- Covariates: Older age and lower education were associated with poorer test performance. Age was the strongest covariate (see **Figure 3**). Results support the use of age-adjusted test norms.
- Measure equivalence: Compared with psychometric properties of these tests in samples from the United States, results from Russia were in the same direction and of similar magnitude, though with variability for some tests. Specifically, time to completion for **Trails B** was slower in Russia compared to US-based normative data, perhaps due to differences between United States and Russia in the use of over-learned alphabetical sequences.

Figure 3. Number of Cognitive Tests With Significant *P*-values for Age, Education, and Gender



Conclusions

- The Russian translation/adaptation of the TOMMORROW neuropsychological battery is psychometrically sound and performs comparably to English test versions with few exceptions.
- Variability between United States and Russia on some tests highlights the need for region-specific norms.
- Given adequate reliability and validity, age-corrected normative data were developed for use with Russian-speaking participants in the TOMMORROW Study.
- The use of this standardized battery and normative data will enhance precision for measuring cognition and treatment effects in Russia and will facilitate the detection of cases of mild cognitive impairment in AD continuum clinical trials.

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