Journal of Alzheimer's Disease 29 (2012) 1–5
IOS Press

Supplementary Data

Effect of Homocysteine Lowering Treatment on Cognitive Function: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Accepted 19 November 2011

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ISSN 1387-2877/12/$27.50

Supplementary Table 1
Cognitive function tests used in the randomized trials

Domain	Test	Description	Study
General cognitive function	ADAS-cog [1]	The cognitive section of the Alzheimer's Disease Scale. It consists of 11 items yielding a maximum score of 70. Lower scores indicate better cognitive function	Aisen, Clarke, Ford
	MMSE [2]	The most widely used test of cognitive function. It tests in 5 areas: memory, language, visuospatial skills, attention/calculation, and orientation. Maximum score is 30 with scores of < 24 indicating significant impairment	Aisen, Clarke, Connelly, de Jager, Ford, Garcia, Hvas, Kwok, McMahon, Seal
	MDRS [3]	A test of general cognition using a combination of tasks and stimulus cards. It yields an overall score as well as sub-scores in 5 domains: attention, initiation-perseveration, construction, conceptualization, and memory	Kwok
	CAMCOG [4]	The cognitive section of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX). Total score of 105 with sub-scores for various cognitive domains. Age and education appropriate normative values are available	Hvas
	TICS [5]	A relatively brief screening test designed to be administered by phone. The common form consists of 13 items yielding a maximum score of 39	Kang, Stott
Memory	RMT [6]	Measures a broad range of memory functions including cognitive and attention efficiency. It takes approximately 20 minutes and comprises five different parallel forms of acquisition, recall, and memory subtests	Fioravanti
	MDRS – memory [3]	Memory domain of MDRS	Kwok
	RAVLT [7]	Immediate recall of 15 nouns read out in 5 trials. Recall of the 15 nouns after a second 15 –noun list is read out and then identify the 30 nouns from a list of 50	Bryan, McMahon
	Digit-symbol-coding recall (WAIS-III) [8]	Participants asked to complete digit-symbol substitutions on a printed sheet. Recall of symbol-digit pairs scored for this task	Bryan
	Activity recall	Participants asked to recall the 13 cognitive tasks completed in the study	Bryan
	Sperling whole report [9]	Thirty slides of 12 random letters presented briefly and subjects asked to report as many as possible	Deijen
	Associate learning task [10]	Participants have to recall the occupation of 9 name and occupation pairs	Deijen
	Associate recognition task [10]	Participant is asked to recall the name and occupation after a 1-hour delay	Deijen
	Visual memory task [10]	Recognition of 9 picture slides from 15 slides presented after a 1-hour delay	Deijen
	Word learning test [11]	Read and memorize 15 monosyllabic words with immediate and delayed (20 minutes) recall	Durga
	Figure of Rey, immediate recall [12]	Draw the figure of Rey immediately after copying it from an example	Eussen
	Figure of Rey, delayed recall [12]	Draw the figure of Rey after a delay of 30 minutes	Eussen
	15 word learning, immediate recall [13]	Read 15 words 5 times and recall words in between readings	Eussen
	15 word learning, delayed recall [13]	Recall the words of the 15 word-learning test	Eussen
	15 word learning, recognition [13]	Recognize the original 15 words from a list of 30	Eussen
	CVLT, immediate recall [14]	A list of 16 words is read allowed in 5 trials and participants are asked to recall these immediately thereafter	Ford, Garcia
	CVLT, delayed recall [14]	Recall of the lists of words after a delay of 20 minutes	Ford
	12 word learning, immediate [15]	Immediate recall of a list of 12 words	Hvas

Supplementary Table 1
(*continued*)

Domain	Test	Description	Study
	12 word learning, delayed [15]	Recall of a list of 12 words after a 15-minute delay	Hvas
	East Boston memory test [16]	Subject is read a short paragraph and is asked to recall 12 key elements immediately and after a 15-minute delay	Kang
	Visual reproduction [8]	Reproduction of 4 drawings	Lewerin
	Thurstone's picture memory test [17]	28 pictures presented consecutively and subject asked to identify each picture amongst 4 similar pictures	Lewerin
	Wechsler paragraph recall test [8]	Immediate recall of a paragraph length passage of text	McMahon
	Hopkins Verbal Learning Test – revised delayed recall [18]	A brief assessment of verbal learning and memory. Three learning trials followed by a recall trial after 20–25 minutes	De Jager
Speed of processing/Attention	DSST/Digit-symbol-coding (WAIS-III) [8]	Replace digits with symbols from an existing code in 90 seconds	Bryan, Connelly, Lewerin, Pathansali
	RMT – efficiency [6]	Cognitive and attention efficiency sub tasks of the RMT	Fioravanti
	MDRS – attention [3]	Attention sub-score of the MDRS	Kwok
	Boxes test [19]	Complete as many boxes with a missing side as possible in 30 seconds	Bryan
	Symbol search (WAIS-III) [8]	Scan 2 columns of symbols and indicate whether the symbols of 1 column appear in the other	Bryan
	Concept shifting test [20]	Time taken to cross off 16 circles in numerical and alphabetical order	Durga
	Letter digit substitution test [21]	Add the corresponding digit to letters according to a key	Durga, Stott
	Finger tapping [22]	Press a button as often as possible in 30 seconds (computerized)	Eussen
	Motor planning 2 [22]	Press a lit button out of 3 buttons as fast as possible (computerized)	Eussen
	Digit span forward [8]	Repeat a string of digits in original order	Eussen, Lewerin
	Digit span backward [8]	Repeat a string of digits in reverse order	Eussen, Lewerin
	Digit cancellation test [23]	Cross out target digits in amongst rows of digits on a page. Number correct minus number incorrect in allotted time	Ford
	Identical forms [24]	Pick out the identical figure from 5 alternatives	Lewerin
	Continuous attention test [25]	Computerized test where subject has to respond whenever 2 consecutive patterns are the same	Pathansali
	Four-choice reaction time [25]	Touch a circle matching an illuminated circle as quickly as possible (computerized)	Pathansali
	Scanning memory sets [25]	Identify a number from a set of 3, 4 then 5 numbers (computerized)	Pathansali
Language	Vocabulary (WAIS-III) [8]	Define 15 words	Bryan
	Spot the word [26]	Identify the correct word from a pair	Bryan
	Synonyms [24]	Select a synonym for a given word	Lewerin
Executive function	Stroop [27]	Read colored words out loud and name the color	Bryan, Durga, Eussen, Garcia
	Uses for objects[28]	Say as many different uses for a common object in 90 seconds	Bryan
	Trail making test A [29]	Join 25 numbers in numerical order	Bryan, Eussen
	Trail making test B [29]	Join up alternating numbers and letters in the correct order	Bryan, Eussen, McMahon
	Verbal fluency – initial letter [30]	Generate as many words as possible starting with a given letter. Time limited test	Bryan, Eussen, McMahon
	Verbal fluency – excluded letter [30]	Generate as many words as possible not including a given letter. Time limited test	Bryan
	Verbal fluency – category [30]	Generate as many words as possible from a given category e.g. animals. Time limited test	De Jager, Durga, Eussen, Kang, McMahon

Supplementary Table 1
(*continued*)

Domain	Test	Description	Study
	Motor planning 3 [22]	Inhibit automatic reaction in pressing a button immediately adjacent to a lit button as quickly as possible (computerized)	Eussen
	Raven's matrices [31]	Choose a design that fits into a matrix	Eussen, McMahon
	Similarities (WAIS-III) [8]	State similarities between 5 pairs of nouns	Eussen
	Clock drawing test [32]	Draw a clock face. Score 1 point for circle/square, 1 point for numbers in correct position and 1 point for correct time	Ford
	Figure classification [17]	Choose non-identical picture from a set of 5	Lewerin
	CLOX [33]	Clock drawing task with emphasis on determining patients' executive control	De Jager
Activities of daily living/Dementia severity	CDR [34]	Rates severity of dementia according to 6 domains resulting in scores of 0 (none), 0.5 (possible), 1 (mild), 2 (moderate), or 3 (severe)	Aisen
	ADCS-ADL [35]	23-item scale ratings level of independence and basic functioning. Maximum score is 30	Aisen
	Bristol Activities of daily living [36]	Measures 20 daily living abilities. Designed for use in dementia. Higher scores equal worsened function	Clarke
	IADL of NOSGER [37]	Measure of more complex living abilities	Connelly
Behaviour	NPI [38]	Assesses 10 behavioral disturbances with maximum score of 144	Aisen, Kwok
	Social behavior subscale of NOSGER [37]	Scale to assess behavior and function in elderly patients. Primarily for use is research studies	Connelly
Visuospatial	Complex figure of Rey, copy [12]	Copy the figure of Rey	Eussen
	Block design (WAIS-III) [8]	Construct a design out of blocks	Lewerin

Abbreviations: ADAS-cog - Alzheimer's Disease Assessment Scale-cognitive subscale, MMSE - Mini-Mental State Examination, MDRS – Mattis Dementia Rating Scale, CAMCOG - Cambridge Cognitive Examination, TICS – Telephone Interview of Cognitive Status, RMT – Randt Memory Test, RAVLT – Rey Auditory Verbal Learning Test, WAIS-III - Wechsler Adult Intelligence Test III, CVLT – California Verbal Learning Test, DSST – Digit Symbol Substitution Test, CDR – Clinical Dementia Rating scale, ADCS-ADL - Alzheimer's Disease Cooperative Study - activities of daily living scale, IADL – Instrumental Activities of Daily Living, NPI – Neuropsychiatric Inventory, NOSGER - Nurses' Observation Scale for Geriatric Patients.

REFERENCES

[1] Rosen WG, Mohs RC, Davis KL (1984) A new rating scale for Alzheimer's disease. *Am J Psychiatry* **141**, 1356-1364.

[2] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[3] Chan AS, Choi MK, Salmon DP (2001) The effects of age, education, and gender on the Mattis Dementia Rating Scale performance of elderly Chinese and American individuals. *J Gerontol B Psychol Sci Soc Sci* **56**, P356-P363.

[4] Roth M, Tym E, Mountjoy CQ, Huppert FA, Hendrie H, Verma S, Goddard R (1986) CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Br J Psychiatry* **149**, 698-709.

[5] Knopman DS, Roberts RO, Geda YE, Pankratz VS, Christianson TJ, Petersen RC, Rocca WA (2010) Validation of the telephone interview for cognitive status-modified in subjects with normal cognition, mild cognitive impairment, or dementia. *Neuroepidemiology* **34**, 34-42.

[6] Randt CT, Brown ER (1983) *Randt Memory Test: Administration Manual*, Life Science Associates, Bayport, NY.

[7] Schmidt M (1996) *Rey Auditory Verbal Learning Test: A Handbook*, Western Psychological Services, Los Angeles, LA.

[8] Wechsler DS (1975) *Wechsler Adult Intelligence Scale*, 3rd ed. The Psychological Corporation, Harcourt Brace, San Antonio, Texas.

[9] Sperling G (1960) The information available in brief visual presentation. *Psychol Monogr* **74**, 11.

[10] Emmen H, Hogendijk EMG, Hooisma J, Orlebeke JF, Uijtdehaage SHJ (1988) *Adaptation of two standardized international test batteries for use in the Netherlands for detection of exposure to neurotoxic compounds. Internal report*, Medisch Biologisch Laboratorium TNO, Rijswijk.

[11] Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J (2005) Rey's verbal learning test: Normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc* **11**, 290-302.

[12] Visser R (1985) *Manual of the Complex Figure Test*, Sweets & Zeitlinger, Lisse, Netherlands.

[13] Saan R, Deelman BG (1986) *New 15-word test (A and B): A manual*, Sweets & Zeitlinger, Lisse, Netherlands.

[14] Delis D, Kramer JH, Kaplan E, Ober BA (2000) *California Verbal Learning Test - second edition, adult version*, The Psychological Corporation.

[15] Nielsen H, Lolk A, Krag-Sorensen P (1985) Normative data for eight neuropsychological tests, gathered from a random sample of Danes aged 64–83 years. *Nordisk Psychologi* **47**, 241-255.

[16] Scherr PA, Albert MS, Funkenstein HH, Cook NR, Hennekens CH, Branch LG, White LR, Taylor JO, Evans DA (1988) Correlates of cognitive function in an elderly community population. *Am J Epidemiol* **128**, 1084-1101.

[17] Thurstone L (1938) *Primary mental abilities. Psychometric monographs*, University of Chicago Press.

[18] de Jager CA, Schrijnemaekers AC, Honey TE, Budge MM (2009) Detection of MCI in the clinic: Evaluation of the sensitivity and specificity of a computerised test battery, the Hopkins Verbal Learning Test and the MMSE. *Age Ageing* **38**, 455-460.

[19] Earles JL, Salthouse TA (1995) Interrelations of age, health, and speed. *J Gerontol B Psychol Sci Soc Sci* **50**, P33-P41.

[20] Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J (2006) The Concept Shifting Test: Adult normative data. *Psychol Assess* **18**, 424-432.

[21] Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J (2006) Normative data for the Animal, Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *J Int Neuropsychol Soc* **12**, 80-89.

[22] Houx P (1991) *Cognitive aging and health-related factors*, Maastricht University, Maastricht, Netherlands.

[23] Spinnler H, Tognoni G (1987) Standardizzazione e Taratura Italiana di Test Neuropsicologici. *Ital J Neurol Sci* **6**, 47-50.

[24] Dureman I, Salde H (1959) *Psychometric and experimental psychological methods for clinical application*, Almqvist & Wiksell, Stockholm, Sweden.

[25] Kalra L, Jackson SH, Swift CG (1993) Assessment of changes in psychomotor performance of elderly subjects. *Br J Clin Pharmacol* **36**, 383-389.

[26] Baddeley A, Emslie H, Nimmo-Smith I (1988) Estimating premorbid intelligence. *J Clin Exp Neuropsychol* **10**, 326.

[27] Dodrill CB (1978) A neuropsychological battery for epilepsy. *Epilepsia* **19**, 611-623.

[28] Getzels J, Jackson PW (1962) *Creativity and Intelligence*, Wiley, New York, NY.

[29] Reitan R, Wolfson D (1985) *The Halstead-Reitan Neuropsychological Test Battery*, Neuropsychology Press, Tucson, Arizona.

[30] Benton A, Hamsher K (1989) *Multilingual Aphasia Examination*, AJA, Iowa City, Iowa.

[31] Raven J (1965) *Guide to using the Coloured Progressive Matrices*, HK Lewis, London, UK.

[32] Brodaty H, Moore CM (1997) The Clock Drawing Test for dementia of the Alzheimer's type: A comparison of three scoring methods in a memory disorders clinic. *Int J Geriatr Psychiatry* **12**, 619-627.

[33] Royall DR, Cordes JA, Polk M (1998) CLOX: An executive clock drawing task. *J Neurol Neurosurg Psychiatry* **64**, 588-594.

[34] Morris JC (1993) The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology* **43**, 2412-2414.

[35] Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, Ferris S (1997) An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* **11**(Suppl 2), S33-S39.

[36] Bucks RS, Ashworth DL, Wilcock GK, Siegfried K (1996) Assessment of activities of daily living in dementia: Development of the Bristol Activities of Daily Living Scale. *Age Ageing* **25**, 113-120.

[37] Spiegel R, Brunner C, Ermini-Funfschilling D, Monsch A, Notter M, Puxty J, Tremmel L (1991) A new behavioral assessment scale for geriatric out- and in-patients: The NOSGER (Nurses' Observation Scale for Geriatric Patients). *J Am Geriatr Soc* **39**, 339-347.

[38] Cummings JL (1997) The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology* **48**, S10-S16.