# **Online Data Supplement**

**Title:** Detection of mild cognitive impairment in middle-aged and older adults with obstructive sleep apnea.

#### **Authors:**

Katia Gagnon, BSc

Andrée-Ann Baril, BSc

Jacques Montplaisir, MD, PhD

Julie Carrier, PhD

Sirin Chami, BSc

Serge Gauthier, MD

Chantal Lafond, MD

Jean-François Gagnon, PhD

Nadia Gosselin, PhD

#### **DETAILED METHODS**

### **Participants**

The following recruitment methods were used: reference from the Department of Pulmonology of the Hôpital du Sacré-Coeur de Montréal (n=35), newspaper ads asking volunteers for a study on sleep and cognitive health (n=63) and reference from other laboratories based on suspected obstructive sleep apnea (OSA) (n=33). We included participants aged between 55 and 85 years, with at least 7 years of education, without neuropsychological evaluation in the last year, and with French or English as their mother tongue. We excluded participants with a diagnosis of dementia based on the neuropsychological assessment (see Table E1), sleep disorders other than OSA (e.g. insomnia, restless leg syndrome, narcolepsy, rapid eye movement sleep behavior disorder), morbid obesity (body mass index >40 kg/m²), and neurological (e.g. Parkinson's disease, previous stroke, brain tumors, epilepsy) or psychiatric disorders (e.g. diagnosed major depression and anxiety disorder). The use of medication (e.g., hypnotics, antidepressants, anticonvulsants, opioids) and/or drugs known to affect cognition, sleep, or cerebral functioning also led to exclusion.

### **Questionnaires**

Because they may be associated with increased risk of MCI [1-9], we documented conditions such as depression and anxiety symptoms, poor sleep quality and cardiovascular diseases using the following instruments: the Beck Depression Inventory-II [10], the Beck Anxiety Index [11], the Pittsburgh Sleep Quality Index [12], and the Epworth Sleepiness Scale [13, 14], the Activities of Daily Living Inventory filled by patients themselves and/or relatives [15], and the Vascular Burden Index [16].

#### Sleep data acquisition and analysis

All participants had a full-night in-laboratory polysomnographic recording. This protocol was extensively described in previous studies [17-19]. Briefly, we used 18 electroencephalographic channel montage combined with electrooculograms, electromoyograms and electrocardiogram. We monitored respiration with thoraco-abdominal strain gauges, an oronasal thermistor and a canula, in addition to a transcutaneous finger pulse oximeter to measure oxygen saturation. Sleep and respiratory events were scored according to the standard method [20, 21]. Apneas and hypopneas were summed and divided by the total hours of sleep to create the apnea-hypopnea index.

# Neuropsychological procedure

We first administered the Montreal Cognitive Assessment (MoCA), followed by the Mini-Mental State Examination (MMSE) and all other neuropsychological tests. Questions related to orientation, such as date, month, year, day of the week, place, and city, were asked only during the MoCA. We then added the orientation score to the MMSE. According to the MoCA standard procedure, an extra point was given to participants with 12 years of education or less. Neuropsychological tests and measures were selected to assess five cognitive domains: 1) attention and speed processing; 2) executive functions; 3) visual and verbal episodic learning and memory; 4) visuospatial abilities; 5) language. All neuropsychological tests, normative data and selected measures, as well as criteria to define mild cognitive impairment (MCI) are presented in Table E1.

# **TABLES**

 Table E1. Neuropsychological tests and variables used to identify MCI.

Tests	Variables	Criteria for domain
		impairment
Attention and spee	d processing	
CPT-II [22]	Omission % (T score) [22]	
	Variability of standard error (T score) [22]	
CWIT [23]	Part 1 (time) [23]	2/5 results ≥1.5 SD
Coding [24]	Scale score [24]	
TMT [25]	Part A (time) [26]	
Executive function	2.S	
Digit Span [24]	Backward (scale score) [24]	
TMT [25]	Part B - Part A (time) [26]	
CPT-II [22]	Commission % (T score) [22]	
CWIT [23]	Part 3 – Part 1 (scale score time) [23]	2/7 results ≥1.5 SD
	Part 4- Part 3 (scale score time) [23]	
TOL [27]	Total move [27]	
	Total time [27]	
Verbal and visual	episodic learning and memory	
RAVLT [28]	Sum of trials 1 to 5 [29]	
	List B [29]	2/7 results ≥1.5 SD
	Delayed recall [29]	
	Delayed recognition [29]	

BVMT-R [30] Total recall (trials 1 to 3) [30]

Delayed recall [30]

Discrimination index [30]

Visuospatial abilities			
ROCF [31]	Copy score [32, 33]		
BLOJ [34]	Number of correct answers [34]	2/4 results ≥1.5 SD	
Bells test [35]	Number of omission [35]		
Blocs [24]	Scale score [24]		
Language			
BNT [36]	Number of correct answers [36]	2/4 results ≥1.5 SD	
Vocabulary [24]	Scale score [24]		
Verbal fluency [23]	Phonemic (number of words) [23]		
	Semantic (number of words) [37]		

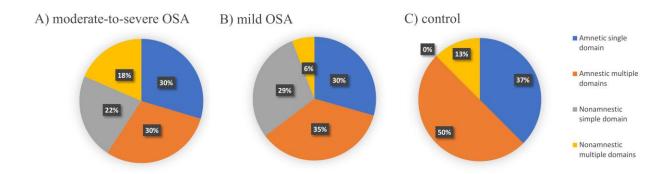
BLOJ, Benton Line Orientation Judgment; BNT, Boston Naming Test; BVMT-R, Brief

Visuospatial Memory Test-revised; CPT-II, Continuous Performance Test – II, CWIT, Color
Word Interference test; MCI, mild cognitive impairment; RAVLT, Rey Auditory Verbal

Learning Test; ROCF, Rey-Osterrieth Complex Figure; SD, standard deviation; TMT, Trail

Making Test; TOL, Tower of London.

Figure E1. Proportions of MCI subtypes in (A) moderate-to-severe OSA, (B) mild OSA, and (C) control participants.



We observed a similar proportion of amnestic single domain between (C) the control (37%), (B) mild OSA (30%) and (A) moderate-to-severe OSA (30%) groups. The proportion of nonamnestic simple domain was similar in the mild OSA (29%) and the moderate-to-severe OSA (22%) groups, but there was no nonamnestic simple domain in the control group (0%). A higher proportion of amnestic multiple domains was observed for the control group (50%) compared to the mild OSA (35%) and the moderate-to-severe OSA (30%) groups. Inversely, we observed a lower proportion of nonamnestic multiple domains for the control and mild OSA participants compared to the moderate-to-severe OSA group. However, we found no significant group differences according to the type (amnestic versus non-amnestic) or number (single versus multiple) of cognitive domains impaired.

## References

- 1. Harris M, Glozier N, Ratnavadivel R, Grunstein RR. Obstructive sleep apnea and depression. Sleep Med Rev. 2009/07/15 ed, 2009.
- 2. Kjelsberg FN, Ruud EA, Stavem K. Predictors of symptoms of anxiety and depression in obstructive sleep apnea. *Sleep Med* 2005: 6(4): 341-346.
- 3. Vaessen TJ, Overeem S, Sitskoorn MM. Cognitive complaints in obstructive sleep apnea. *Sleep Med Rev* 2015: 19: 51-58.
- 4. Saunamaki T, Jehkonen M. Depression and anxiety in obstructive sleep apnea syndrome: a review. *Acta Neurol Scand* 2007: 116(5): 277-288.
- 5. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA* 2004: 291(16): 2013-2016.
- 6. Daulatzai MA. Evidence of neurodegeneration in obstructive sleep apnea: Relationship between obstructive sleep apnea and cognitive dysfunction in the elderly. *J Neurosci Res* 2015: 93(12): 1778-1794.
- 7. Cherbuin N, Reglade-Meslin C, Kumar R, Jacomb P, Easteal S, Christensen H, Sachdev P, Anstey KJ. Risk factors of transition from normal cognition to mild cognitive disorder: the PATH through Life Study. *Dement Geriatr Cogn Disord* 2009: 28(1): 47-55.
- 8. Beaulieu-Bonneau S, Hudon C. Sleep disturbances in older adults with mild cognitive impairment. *Int Psychogeriatr* 2009: 21(4): 654-666.
- 9. Mendonca MD, Alves L, Bugalho P. From subjective cognitive complaints to dementia: who is at risk?: a systematic review. *Am J Alzheimers Dis Other Demen* 2016: 31(2): 105-114.
- 10. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961: 4: 561-571.
- 11. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988: 56(6): 893-897.
- 12. Buysse DJ, Reynolds CFr, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989: 28(2): 193-213.
- 13. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991: 14(6): 540-545.
- 14. Kaminska M, Jobin V, Mayer P, Amyot R, Perraton-Brillon M, Bellemare F. The Epworth Sleepiness Scale: self-administration versus administration by the physician, and validation of a French version. *Canadian respiratory journal* 2010: 17(2): e27-34.
- 15. Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, Ferris S. 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* 1997: 11 Suppl 2: S33-39.
- 16. Villeneuve S, Massoud F, Bocti C, Gauthier S, Belleville S. The nature of episodic memory deficits in MCI with and without vascular burden. *Neuropsychologia* 2011: 49(11): 3027-3035.
- 17. Gosselin N, De Beaumont L, Gagnon K, Baril AA, Mongrain V, Blais H, Montplaisir J, Gagnon JF, Pelleieux S, Poirier J, Carrier J. BDNF Val66Met

- polymorphism interacts with sleep consolidation to predict ability to create new declarative memories. *J Neurosci* 2016: 36(32): 8390-8398.
- 18. Baril AA, Gagnon K, Arbour C, Soucy JP, Montplaisir J, Gagnon JF, Gosselin N. Regional cerebral blood flow during wakeful rest in older subjects with mild to severe obstructive sleep apnea. *Sleep* 2015: 38(9): 1439-1449.
- 19. Baril AA, Gagnon K, Brayet P, Montplaisir J, De Beaumont L, Carrier J, Lafond C, L'Heureux F, Gagnon JF, Gosselin N. Gray Matter Hypertrophy and Thickening with Obstructive Sleep Apnea in Middle-aged and Older Adults. *Am J Respir Crit Care Med* 2017: 195(11): 1509-1518.
- 20. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification. American Academy of Sleep Medicine, Westchester, IL., 2007.
- 21. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012: 8(5): 597-619.
- 22. Conners CK. Conners' Continuous performance Test (CPT-2) computer program for windows, technical guide, and software manual. Multi Health Systems Inc., Toronto, ON, 2000.
- 23. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D-KEFS). The Psychological Corporation, San Antonio, TX, 2001.
- 24. Wechsler D. Wechsler Adult Intelligence Scale-Third Edition. The Psychological Corporation, San Antonio, TX, 1997.
- 25. Army Individual Test Battery: Manual of Directions and Scoring. War Departement, Adjutant General's Office, Washington, DC, 1944.
- 26. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol* 2004: 19(2): 203-214.
- 27. Culbertson WC, Zillmer EA. Tower fo London-Drexel University, second edition. Multi-Health Systems, Toronto, ON, 2004.
- 28. Rey A. L'examen psychologique dans les cas d'encéphalopathie traumatique. *Arch Psychol* 1941: 28(112): 286-340.
- 29. Schmidt M. Rey Auditory-Verbal Learnin Test. Western Psychological Services, Los Angeles, CA, 1996.
- 30. Benedict RHB. Brief visuospatial memory test revised: Professionnal manual. Psychological Assessment Ressources, Inc, Lutz, FL, 1997.
- 31. Osterrieth P. Le test de copie d'une figure complexe. *Arch Psychol* 1944: 30: 206-356.
- 32. Strauss E, Sherman, E.M., Spreen, O. A compendium of neuropsychological tests: administration, norms, and commentary. Oxford University Press, New York, NY, 2006.
- 33. Machulda MM, Ivnik RJ, Smith GE, Ferman TJ, Boeve BF, Knopman D, Petersen RC, Tangalos EG. Mayo's Older Americans Normative Studies: Visual Form Discrimination and copy trial of the Rey-Osterrieth Complex Figure. *J Clin Exp Neuropsychol* 2007: 29(4): 377-384.

- 34. Qualls CE, Bliwise NG, Stringer AY. Short forms of the Benton Judgment of Line Orientation Test: development and psychometric properties. *Arch Clin Neuropsychol* 2000: 15(2): 159-163.
- 35. Gauthier L, Dehaut F, Joanette Y. The Bells Test: A quantitative and qualitative test for visual neglect. *J Clin Exp Neuropsychol* 1989: 11(2): 49-54.
- 36. Kaplan E, Goodglass H, Weintraub S. Boston Namig Test. Lee & Febiger, Philadelphia, PA, 1983.
- 37. Lucas JA, Ivnik RJ, Smith GE, Bohac DL, Tangalos EG, Graff-Radford NR, Petersen RC. Mayo's older Americans normative studies: category fluency norms. *J Clin Exp Neuropsychol* 1998: 20(2): 194-200.