Online-Only Text

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1. Supplemental Table S1

Table S1: Neuropsychological Testing Results 16 Weeks After Onset of Opioid-Associated Amnestic Syndrome

Domain	Test	Raw Score	Errors/Intrusions	Percentile
Global	MMSE	24/30	Delayed recall (0/3), Orientation (7/10)	---
Memory	CVLT-II-SF 9-item			
	Trial 1	4/9	2 intrusions	4th%
	Trial 2	6/9		
	Trial 3	7/9		
	Trial 4	7/9		
	30-second recall	6/9	2 intrusions	1st%
	10-minute recall	0	0 intrusions	1st%
	Cued recall	4/9	6 intrusions	2nd%
	Recognition	9/9	13 false positive	1st%
	Discrimination Index	1.0	*n/a*	1st%
	WMS-IV Logical Memory			5th%
	Logical Memory-I	14/50	*n/a*	<1st%
	Logical Memory-II	0	*n/a*	<1st%
	Recognition	14/30	*n/a*	---
	BVMT-R 12-item			
	Trial 1	4/12	*n/a*	1st%
	Trial 2	5/12	*n/a*	1st%
	Trial 3	5/12	*n/a*	1st%
	25-minute recall	3/12	*n/a*	1st%
	Recognition	5/6	5 false positives	<1st%
	Discrimination Index	1.0	*n/a*	<1st%
	Odor Memory			
	10-minute recognition	5/5	4 false positives	---
	Autobiographical Memory Interview			
	Childhood			
	Semantic	20/21	*n/a*	Normal
	Episodic	8/9	*n/a*	Normal
	Early Adult Life			
	Semantic	19.5/21	*n/a*	Normal
	Episodic	9/9	*n/a*	Normal
	Recent Life			
	Semantic	18/21	*n/a*	Borderline
	Episodic	9/9	*n/a*	Normal
	Total			
	Semantic	57.5/63	*n/a*	Normal
	Episodic	26/27	*n/a*	Normal
Executive Function	WAIS-IV Digit Span			
	Forward – Total	14	*n/a*	91st%
	Forward – Longest	8	*n/a*	---
	Backward – Total	13	*n/a*	98th%
	Backward - Longest	7	*n/a*	---
	Lexical Fluency			68th%
	F words in 60 seconds	25	None	---
	A words in 60 seconds	19	None	---

	S words in 60 seconds	27	None	---
	DKEFS Design Fluency			
	Filled	12	1 repetition	75th%
	Switching	9	2 repetitions, 2 intrusions	63rd%
	Trails B	43 seconds	None	55th%
Processing Speed	Trails A	18 seconds	None	68th%
	Symbol Digit Modalities Test	47	None	16th%
Visuospatial Function	NAB Visual Discrimination	18/18	*n/a*	81st%
	BVMT-R Copy	12/12	*n/a*	---
Language	Boston Naming Test	57/60	1 phonemic cue	37th%
	Semantic Fluency			
	Animals in 60 seconds	18	None	6th%
	Vegetables in 60 seconds	11	None	10th%
Mood/Social Function	Beck Depression Inventory-II	41/63	*n/a*	Severe
	Beck Anxiety Inventory	32/63	*n/a*	Severe
	TASIT Emotion Evaluation Test	12/16	*n/a*	73rd%

Note: MMSE = Mini-mental state exam; BVMT-R = Brief Visual Memory Test, revised; CVLT-II-SF = California Verbal Learning Test; DKEFS = Delis-Kaplan Executive Function System; NAB = Neuropsychological Assessment Battery; TASIT = The Awareness of Social Inference Test; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale. For further explanation of individual tests and references, see supplemental *Section 4*.

2. Neuropsychological battery

1. Mini Mental Status Examination (MMSE)[1]: 30-item screener of global cognition.
2. California Verbal Learning Test, 2nd edition, short form (CVLT-II-SF)[2]: Participants are asked to recall a 9-item list of semantically-related words (four semantic categories) immediately across four learning trials. Participants are then asked to freely recall the list of items after a 30-second interference task and again after a 10-minute delay. After the long delay recall, participants are additionally asked to recall the items given semantic cueing and discriminate between words that were on the original list or not on the list via a 36-item recognition probe. This is a measure of unstructured verbal episodic memory.
3. Wechsler Memory Scale, fourth edition, Logical Memory (WMS-IV)[3]: Participants are asked to recall two separate stories immediately after a learning trial, and again after a 20-30 minute delay. After the long delay recall, participants are also given yes/no recognition items regarding the content of the stories. This is a measure of structured verbal episodic memory.
4. Brief Visual Memory Test, revised (BVMT-R)[4]: Participants are shown an array of six figures for 10-seconds and asked to immediately draw the array after the exposure; this is repeated over three learning trials. Participants are then asked to freely draw the figures after a 25-30-minute delay and identify correct item elements from a multiple-choice format. Items are scored for accuracy of drawing and spatial placement within the array. This is a measure of visuospatial episodic memory. Participants are also asked to copy the array at the end of all recall trials to assess for primary visuoconstructional abilities.
5. Autobiographical Memory Interview (AMI)[5]: Participants are asked as series of questions concurrently probing a) autobiographical incidents, and b) personal semantic memory. For autobiographical incidents, participants are asked to produce specific memories (e.g., *What is a memory from primary school?*), as well as answer semantic information (e.g., *What was your childhood address?*) from time epochs evaluated from birth to current. Items are scored with regard to specificity (autobiographical incidents) or accuracy (semantic memory).
6. Delis-Kaplan Executive Functions System (DKEFS) Design Fluency[6]: In the Filled Dots condition, participants are presented with a page of boxes, each containing the same array of five filled dots. They are asked to draw four-line designs that do not repeat for 60-seconds. In the Switching condition, participants are presented with a page of boxes, each containing the same array of five filled and five empty dots. Again, participants are asked to draw four-line designs that do not repeat for 60-seconds but must now switch between empty and filled dots for each sequence. This is a measure of executive functions, tapping into visual generativity, self-monitoring (e.g., via error analysis), and set-shifting (i.e., Switching condition).
7. Trail Making Test (TMT), parts A and B[7]: In part A of the TMT, participants are asked to draw lines sequencing an array of numbers in consecutive, ascending order as fast as possible. In part B, participants are presented with an array of numbers and letters and are asked to alternate between connecting the

number and letters in consecutive, ascending order as fast as possible. This is a measure of executive functions, tapping into visual processing speed (Trails A) and set-shifting (Trails B).

8. Wechsler Adult Intelligence Test, fourth edition, Digit Span (WAIS-IV)[8]: In Digit Span Forwards, participants are asked to immediately repeat a series of numbers that are said aloud to the participant. The string of numbers becomes increasingly longer with each trial. In Digit Span Backwards, participants are asked to say a series of numbers in reverse order immediately after they are said to him/her, again with increasing span over trials. Digit Span Forwards assesses echoic store/phonological loop, while Digit Span Backwards assesses working memory (a component of executive functions).

9. Symbol Digit Modalities Test[9]: Participants are asked to substitute geometric symbols for numbers using a response key for 120-seconds. This is primarily a measure of visual speed of processing.

10. Neuropsychological Assessment Battery (NAB) Visual Discriminations[10]: Participants are presented with a target figure and asked to match the target figure with one of four options below. This is a measure of visuospatial processing.

11. Boston Naming Test[7]: Participants are asked to name a pictured object. If the picture is not freely named, a phonemic cue is given (first phoneme of the word), and/or a multiple-choice option with two foil words. This is a measure of confrontation naming.

12. Controlled Oral Word Association Task (COWAT)[7]: Participants are given a letter of the alphabet and asked to name as many words as possible that begin with that letter for 60-seconds (F-A-S). This is a measure of executive functions, specifically assessing lexical fluency/verbal generativity.

13. Semantic fluency[7]: Participants are given a category and asked to name as many words as possible that belong to that category for 60-seconds (e.g., Animals). This is a measure of language functioning, specifically assessing semantic generativity.

14. Beck Depression Inventory, second edition (BDI-II) [11]: This is a 21-item self-reported measure in which participants are asked to rate the presence and severity of depressive symptoms.

15. Beck Anxiety Inventory (BAI)[12]: This is a 21-item self-reported measure in which participants are asked to rate the presence and degree of anxiety symptoms in the past week. Items include both cognitive and somatic symptoms of anxiety.

16. The Awareness of Social Inference Test (TASIT) Emotion Evaluation Test[13]: Participants are shown a series of brief (20-30 seconds) emotionally-salient videos that have little semantic meaning and are asked to identify the emotion presented from a list displayed on the screen (disgust, happiness, sadness, fear, anger, surprise, or no emotion). This is a measure of social-emotional functioning.

3. Imaging protocols

At 4 months post event, a structural brain MRI scans was acquired at the UCSF Neuroscience Imaging Center on a 3-Tesla Siemens TIM Trio scanner equipped with a 12-channel head coil. A 3D volumetric magnetization prepared rapid gradient-echo MRI (MPRAGE) was obtained
(TR/TE/TI = 2300/2.98/900 milliseconds) with 9° flip angle. The field of view was 256×256 mm with 1×1 mm in-plane resolution and 1 mm slice thickness. Additional sequences included: T-2 weighted sequences with thin cuts through mesial temporal structures, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted images/apparent diffusion coefficient maps (DWI/ADC; B2500 and B1000), and susceptibility weighted images. A premorbid scan was completed one week prior to the seminal event. An MPRAGE equivalent protocol with 3D axial T-1 weighted spoiled gradient-recall echo (SPGR) images was obtained on a General Electric 3-Tesla Signa HDxt scanner equipped with an 8-channel head coil (TR/TE/TI = 7888/3.00/450 milliseconds) with 12° flip angle, 256 x 256 mm field of view, 1x1 mm in-plane resolution and 1 mm slice thickness. Scans were visually inspected for artifact and quality prior to computational evaluation. The open source software Statistical Parametric Mapping (SPM8/SPM12; http://www.fil.ion.ucl.ac.uk/spm/) provided the segmentation engine to parse constituent images into gray matter, white matter, and cerebrospinal fluid within templated space. Automated hippocampal volume calculations were performed on 3D T-1 weighted MPRAGE/SPGR segmented images by way of a reliable and well-validated algorithm (see *references 5* and *6* from manuscript). Stated briefly, hippocampal gray matter volume was ascertained by applying a binary hippocampal mask with 1-mm isotropic resolution to the normalized and modulated gray matter segmented image (see https://www.fil.ion.ucl.ac.uk/spm/ext/#HV). Hippocampal structures included the *cornu ammonis*, fascia dentata, and subiculum (see *references 7* and *8* from manuscript). Total intracranial volume was estimated as a sum of gray and white matter plus cerebral spinal fluid volume. To confirm the reliability of the computational volumetric method, we calculated and compared total intracranial and hippocampal volumes from the in-patient structural brain MRI performed 8 days after the pre-morbid scan.

Volumetry was performed on 3D axial T-1 weighted SPGR images which were obtain on a General Electric 1.5-Tesla Signa HDxt scanner with an 8-channel head coil (TR/TE/TI = 9.884/3.888/350 ms) with 15° flip angle, 256 x 256 mm field of view, 1x1 mm in-plane resolution and 1 mm slice thickness. Hippocampal gray matter volume (*cornu ammonis* + fascia dentata) was 4.1722 and 3.7911 ml on the left and right, respectively (sum = 7.9633 ml). Hippocampal volumes which included the subiculum subfield were 6.2168 and 5.8554 ml on the left and right, respectively (sum = 12.0722 ml). Total intracranial volumes differed by ~1% pre- and post-morbid, 1745.5589 ml and 1764.6615 ml, respectively. Similarly, total gray matter volumes differed by ~1% pre- and post-morbid, 837.5098 ml and 848.7063 ml, respectively. As a confirmatory step for the data processing approach we compared pre-morbid total intracranial volume with that obtained by the acute scan 8 days later when the patient was hospitalized. Scan/re-scan results for total intracranial volumes differed by less than 0.02%, which supports the reliability of the method. 3-dimensional hippocampal constructions (Figure 3) were generated with the open-source software, ITK-SNAP (http://www.itksnap.org/pmwiki/pmwiki.php). We applied a semi-automated segmentation technique to the raw T-1 weighted imaging data (e.g. *NIfTI* files (https://nifti.nimh.nih.gov/) that masked out all structures except the bilateral *cornu ammonis* + fascia dentata.

4. References

1. Folstein MF. The Mini-Mental State Examination. *Arch Gen Psychiatry*. 1983;40(7):812. doi:10.1001/archpsyc.1983.01790060110016.
2. Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test – second edition. Adult version. Manual. *Test*. 2000.
3. Wechsler D. *Wechsler Memory Scale-Fourth Edition (WMS-IV)*. 4th ed. New York, NY: The Psychological Corporation; 2009.
4. Norman MA, Moore DJ, Taylor M, et al. Demographically corrected norms for African Americans and caucasians on the hopkins verbal learning test-revised, Brief visuospatial memory test-revised, stroop color and word test, and wisconsin card sorting test 64-card version. *J Clin Exp Neuropsychol*. 2011;33(7):793-804. doi:10.1080/13803395.2011.559157.
5. Prebble SC, Addis DR, Tippett LJ. Autobiographical memory and sense of self. *Psychol Bull*. 2013;139(4):815-840. doi:10.1037/a0030146.
6. Delis DC, Kaplan E, Kramer JH. *D-KEFS: Delis-Kaplan Executive Function System*. San Antonio, TX: The Psychological Corporation; 2001.
7. Heaton RK, Miller W, Taylor MJ, Grant I. *Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults*. Psychological Assessment Resources; 2004.
8. Wechsler D. *Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV)*. 4th ed. San Antonio, TX: The Psychological Corporation; 2008.
9. Lezak MD, Howieson DB, Loring DW, Fischer JS. *Neuropsychological Assessment*. USA: Oxford University Press; 2004.
10. Stern R, White T. *Neuropsychological Assessment Battery*. Lutz, FL: Psychological Assessment Resources; 2003.
11. Beck A, Steer RA, Brown GK. *Beck Depression Inventory-II*. San Antonio, TX: The Psychological Corporation; 1996.
12. Steer RA, Beck A. *Beck Anxiety Inventory*. San Antonio, TX: The Psychological Corporation; 1999.
13. Woolley JD, Strobl E V., Sturm VE, et al. Impaired recognition and regulation of disgust is associated with distinct but partially overlapping patterns of decreased gray matter volume in the ventroanterior insula. *Biol Psychiatry*. 2015;78(7):505-514. doi:10.1016/j.biopsych.2014.12.031.