

Diagnosis of minimal hepatic encephalopathy: a systematic review of point-of-care diagnostic tests (**Supplementary Material**)

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Supplementary Table 1: Search Strings by Database

Database	Search string	Filters	References
Medline	<p>("Hepatic Encephalopathy"[Mesh] or "Hepatic Encephalopathy"[ti])</p> <p>And</p> <p>("Inhibitory control test" or "EncephalApp" or "covert" or "minimal" or "sickness impact profile" or "sip" or "critical flicker frequency" or "CFF" or "Psychometric" or "diagnosis" or "sensitivity" or "specificity" or "likelihood ratio" or "predictive value"))</p>	None	2,772
Embase	<p>('Hepatic Encephalopathy'ab,ti or 'portosystemic encephalopathy'ab,ti OR (minimal OR covert OR overt)NEXT/1 encephalopathy)</p> <p>And</p> <p>("Inhibitory control test"ab,ti or "EncephalApp"ab,ti or "sickness impact profile"ab,ti or "critical flicker frequency"ab,ti or "psychometric"ab,ti or "electroencephalogram"ab,ti or "diagnosis"ab,ti or "sensitivity"ab,ti or "specificity"ab,ti or "likelihood ratio"ab,ti or "predictive value"ab,ti))</p>	None	1,017
Scopus	Sentinel ¹⁻¹² and included article search (references citing or cited by)	N/A	776
Cochrane Library	"Hepatic Encephalopathy":ti,ab,kw and ("Inhibitory control test" or "EncephalApp" or "covert" or "minimal" or "sickness impact profile" or "sip" or "critical flicker frequency" or "CFF" or "Psychometric" or "diagnosis" or "sensitivity" or "specificity" or "likelihood ratio" or "predictive value") (Word variations have been searched)	None	259

Supplementary Table 2: Gold Standards Used to Evaluate Point-of-Care Tests

Gold Standards	Components	How it is scored
Psychometric Hepatic Encephalopathy Score (PHES)	<p>Five timed tasks:</p> <p>1-2: Number connection tests -A and B; connect numbers and letters sorted across a page</p> <p>3: Digit symbol test; match numbers with symbols</p> <p>4: Line-tracing test; trace a winding 5 millimeter-wide shape without touching borders. Also scored for accuracy</p> <p>5: Serial-dotting test; dot the center of circles on a page</p>	<p>Each component is scored with reference to the performance by healthy controls in terms of standard deviations (SD) from the mean (Z score). If performance is 1 SD above it is +1; if 1 SD below, it is -1.</p> <p>The overall score is the sum of Z scores: e.g. -3 for $Z \leq -3$. Studies vary on the Z score that defines a positive test.</p>
Standard Psychometric Tests (SPT)	<p>Four timed tasks:</p> <p>1-2: Number connection tests -A and B; connect numbers and letters sorted across a page</p> <p>3: Digit symbol test; match numbers with symbols</p> <p>4. Block Design Test; arrange bicolored blocks into a specific pattern. Also scored for accuracy.</p>	<p>Each component is scored with reference to the performance by healthy controls in terms of standard deviations (SD) from the mean. A positive test is defined as performance impairment beyond two SD of the local healthy control performance in any of the three tests</p>
Critical Flicker Frequency (CFF)	<p>CFF is a bedside test using specialized, commercially available equipment. Patients are subject to pulsing light from 60 Hz downward until their impression of the light transitions from fused to flickering.</p>	<p>Performance is based on the average frequency of 8 trials. Cutoffs on Hz thresholds are based on previous studies in healthy controls.</p>
Inhibitory Control Test (ICT)	<p>ICT is performed on a laptop or desktop computer. The patient is subject to flashing letters every 500 milliseconds and asked to press the spacebar each time an X follows a Y or vice-versa. These 'targets' occur 212 times. On 40 occasions, an X follows X or Y follows Y. These are called 'lures.'</p>	<p>The absolute number of targets and lures clicked is summarized at the completion of the task. Studies have used variable cutoffs to define positive tests. Two adjustments have been used:</p> <ol style="list-style-type: none"> 1. Weighted lures: Lures/(Target accuracy²) 2. Total Lures=$B_1 + B_2 \times \text{Age} + B_3 \times \text{Male_Gender} + B_4 \times \text{Education}$

Supplementary Table 3: Assessment of Quality According to the QUADAS-2 Tool

Test	Study	Risk of Bias				Applicability Concerns		
		Patient Selection	Index Test	Reference Standard	Flow and timing	Patient selection	Index test	Reference standard
ICT	Bajaj 2007	L	U	L	L	L	L	L
	Bajaj 2008	L	L	L	L	L	L	L
	Bajaj 2009	L	U	L	L	L	L	L
	Amodio 2010	U	H	U	L	L	L	L
	Allampati 2012	U	U	L	L	L	L	L
	Bajaj 2012	L	H	H	H	H	L	U
	Taneja 2012	L	U	U	L	L	L	L
	Baran 2012	U	U	U	U	U	L	L
	Bajaj SES 2013	L	H	H	H	H	L	U
	Goldbecker 2013	L	U	U	L	H	L	L
	Sharma 2013	U	U	L	L	H	L	L
	Bajaj 2013	L	U	U	L	H	L	L
	Jaroszewicz 2014	U	U	L	L	U	L	L
	Gupta 2015	L	U	L	H	H	L	L
	Allampati 2016	L	U	U	L	H	L	L
	Ghabril 2017	H	U	H	H	L	H	U
Stroop	Bajaj 2013	L	U	U	L	H	L	L
	Bajaj 2015	L	U	U	L	H	L	L
	Allampati 2016	L	U	U	L	H	L	L
SIP	Nabi 2014	L	U	U	L	L	L	L
	Lauridsen 2016	U	U	U	U	L	L	L
ANT	Campagna 2017	L	L	U	L	L	L	L

H = high, L = low, and U = unclear.

ANT = animal naming test, ICT = Inhibitory Control Test, SIP = sickness impact profile, Stroop = EncephalApp Stroop.

References

1. Allampati S, Duarte-Rojo A, Thacker LR, et al. Diagnosis of Minimal Hepatic Encephalopathy Using Stroop EncephalApp: A Multicenter US-Based, Norm-Based Study. *Am J Gastroenterol* 2016;111:78-86.
2. Amodio P, Del Piccolo F, Marchetti P, et al. Clinical features and survival of cirrhotic patients with subclinical cognitive alterations detected by the number connection test and computerized psychometric tests. *Hepatology* 1999;29:1662-1667.
3. Bajaj JS, Hafeezullah M, Franco J, et al. Inhibitory control test for the diagnosis of minimal hepatic encephalopathy. *Gastroenterology* 2008;135:1591-1600.e1.
4. Bajaj JS, Hafeezullah M, Hammeke TA, et al. Inhibitory control test is a sensitive and inexpensive alternative for the diagnosis of minimal hepatic encephalopathy. *Gastroenterology and Hepatology* 2009;5:6.
5. Amodio P, Ridola L, Schiff S, et al. Improving the inhibitory control task to detect minimal hepatic encephalopathy. *Gastroenterology* 2010;139:510-8, 518.e1-2.
6. Nabi E, Thacker LR, Wade JB, et al. Diagnosis of covert hepatic encephalopathy without specialized tests. *Clin Gastroenterol Hepatol* 2014;12:1384-1389.e2.
7. Weissenborn K, Ennen JC, Schomerus H, et al. Neuropsychological characterization of hepatic encephalopathy. *Journal of hepatology* 2001;34:768-773.
8. Weissenborn K, Scholz M, Hinrichs H, et al. Neurophysiological assessment of early hepatic encephalopathy. *Electroencephalogr Clin Neurophysiol* 1990;75:289-95.
9. Weissenborn K, Rückert N, Hecker H, et al. The number connection tests A and B: Interindividual variability and use for the assessment of early hepatic encephalopathy. *Journal of Hepatology* 1998;28:646-653.
10. Sood GK, Sarin SK, Mahapatra J, et al. Comparative efficacy of psychometric tests in detection of subclinical hepatic encephalopathy in nonalcoholic cirrhotics: search for a rational approach. *Am J Gastroenterol* 1989;84:156-9.
11. Bajaj JS. Current and future diagnosis of hepatic encephalopathy. *Metab Brain Dis* 2010;25:107-10.
12. Patidar KR, Bajaj JS. Covert and Overt Hepatic Encephalopathy: Diagnosis and Management. *Clin Gastroenterol Hepatol* 2015;13:2048-61.