Using the EncephalApp Stroop, a High-Sensitivity Test, to Screen for Covert Hepatic Encephalopathy

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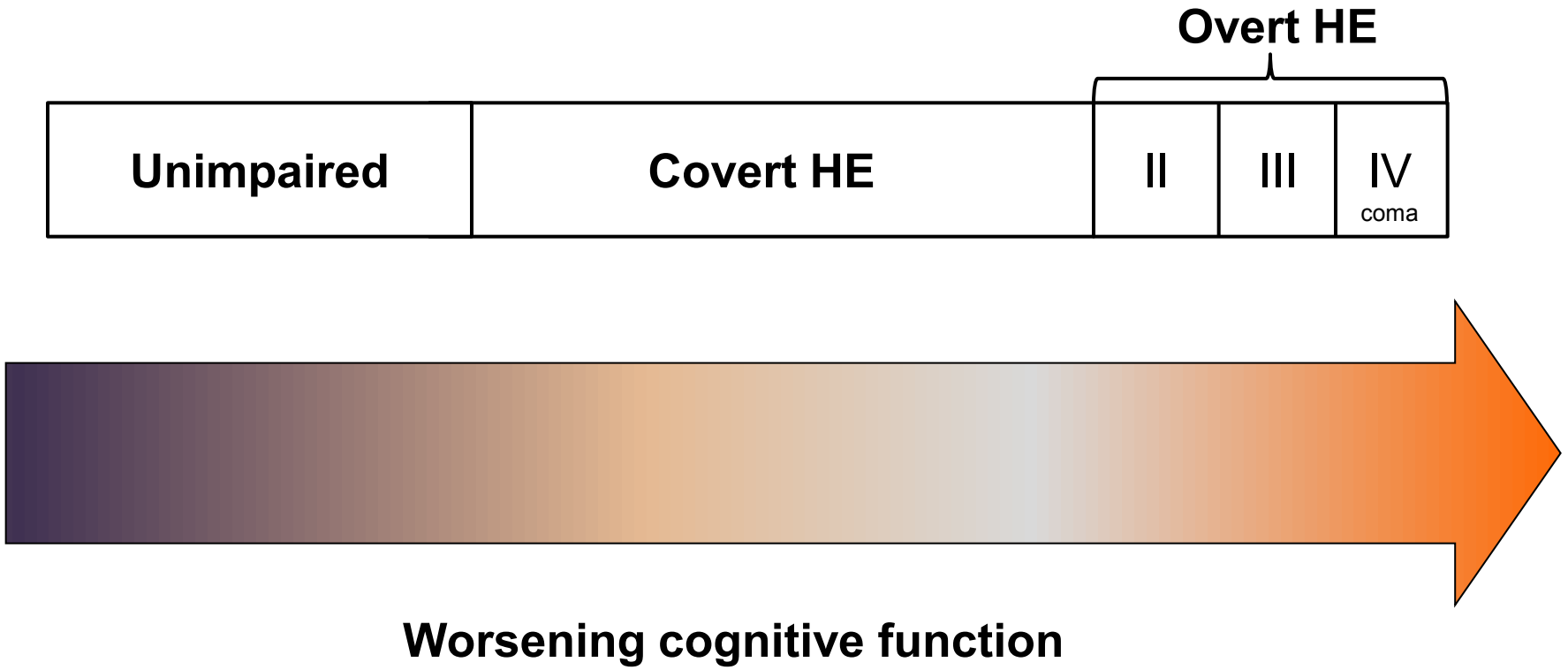
Spectrum of neuro-cognitive impairment in cirrhosis (SONIC)



Bajaj JS et al International Society for Hepatic Encephalopathy and Nitrogen Metabolism *(ISHEN) Consensus Statement Aliment Pharmacol Ther 2011*

Unimpaired, Covert and Overt HE

	Unimpaired	Covert HE	Overt HE
Mental Status	Not impaired	Not impaired	From disorientation through coma
Specialized Tests (according to local expertise)	Not impaired	Impaired	Not specifically required but will be abnormal
Asterixis	None	None	Present (except in coma)

Bajaj JS et al International Society for Hepatic Encephalopathy and Nitrogen Metabolism *(ISHEN) Consensus Statement Aliment Pharmacol Ther 2011*

Covert HE is important to our patients

Outcomes in cirrhotic patients	Affected?
Progression to overt HE	✓
Health-related quality of life	✓
Driving impairment and accidents	✓
Overall survival	✓
Falls	✓
Can be tested for	✓

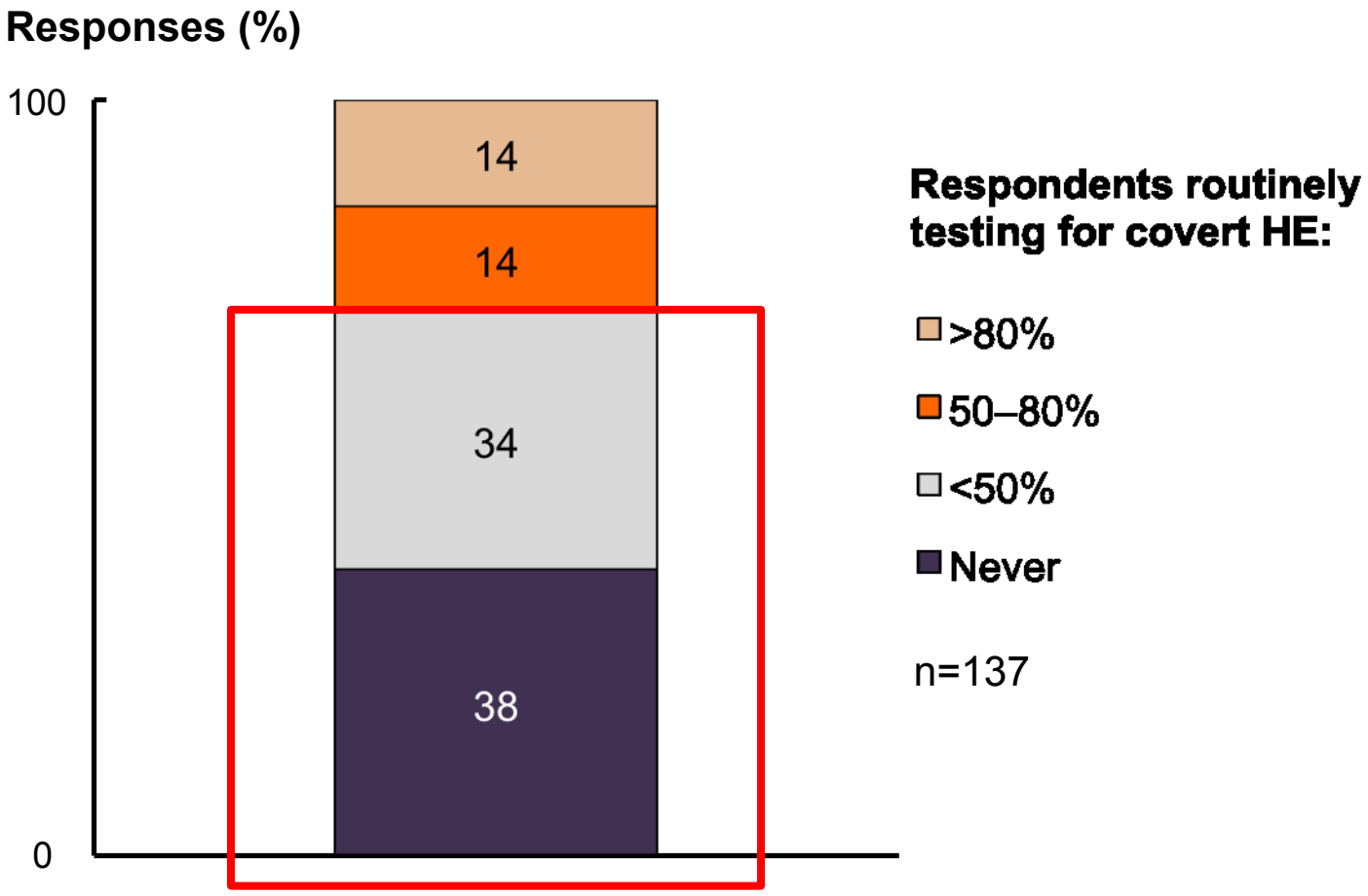
Methods for Detecting Covert HE

Methods	Expense	Time	Validated	Predicting outcomes
Formal psychological assessment	++++	++++	++	++
Neuro/psycho-physiologic tests (EEG, Evoked potential, CFF)	+ - +++	++	++++	++++
Paper-pencil tests (Block design tests, PHES)	+	+	+++	++++
Computerized tests (ICT, SCAN, CDRS, Continuous RT)	+	+	+++	++++

EEG = Electroencephalograph; CFF = Critical Flicker Frequency; PHES = The psychometric hepatic encephalopathy score; ICT = Inhibitory Control Test; CDRS = Cognitive Drug Research (sum of CDR factor score)

Adapted from Mullen KD et al. Semin Liver Dis. 2007

Failure to test for covert HE



Bajaj et al, Hepatology 2007; 45: 833–4

Therefore, brief screening tools for Covert HE are needed

Background

- Brief cognitive screening tools, which do not require psychological expertise in administration and interpretation are needed.
- Stroop tasks have been used to evaluate psychomotor speed and cognitive flexibility
- They are now available as a smartphone app.
- This is the experience of an older app that is now published; the new app that is available on iTunes™ follows the same pattern but cut-offs are likely to differ

Amodio Metab Brain Dis 2005, Felipo Hepatol 2011

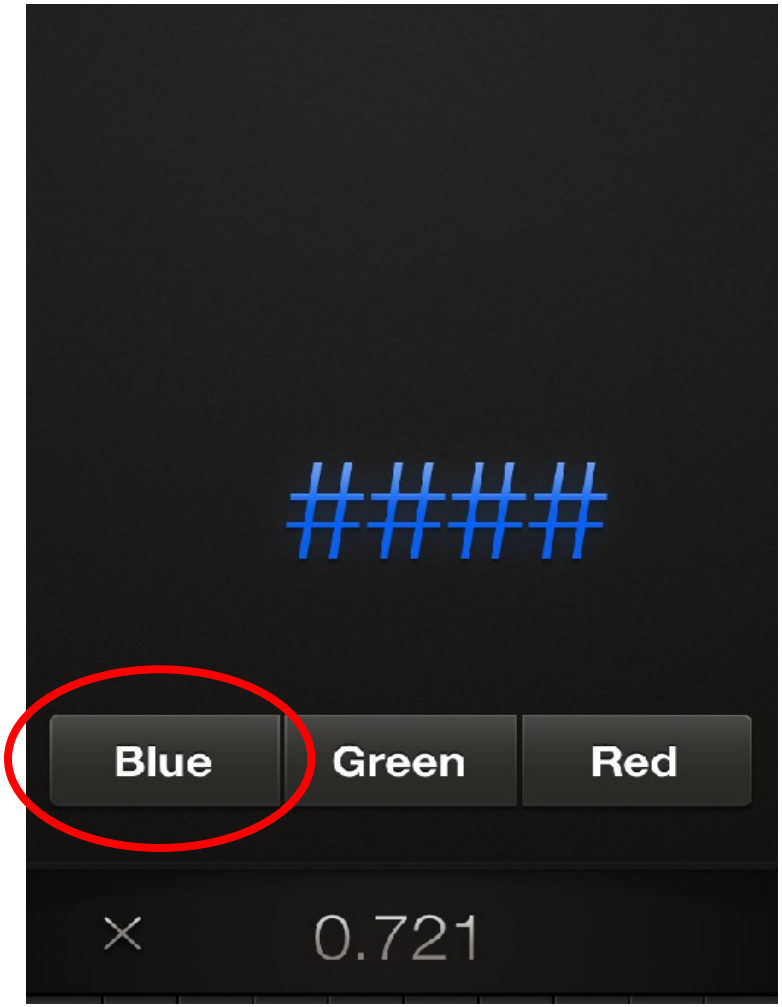
Stroop “Off” State: no words, just symbols

- The task is to correctly and rapidly press the color corresponding to the color of the symbols presented

Presentation of the symbol in a particular color

Touch the correct color

Response Time



Stroop “On” State: Words in discordant colors

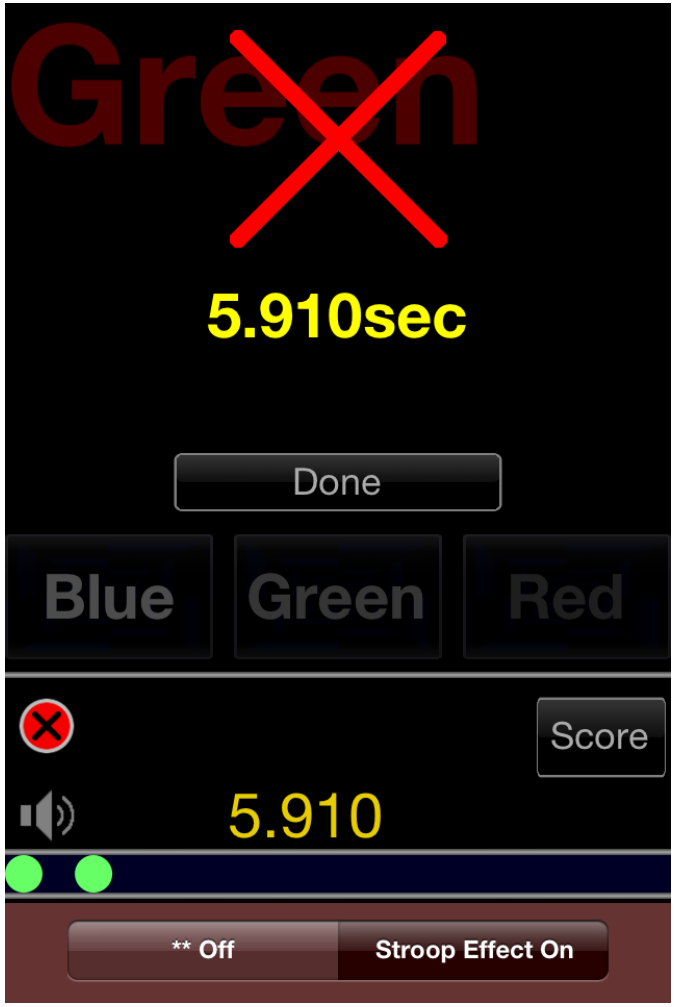
- The task is to correctly and rapidly press the color corresponding to the color of the word presented, not the color it means

Presentation of a word in a discordant color

Touch the correct color of the word, not what the word means

Response Time

Stroop Ourtputs



- Each run has 10 stimuli
- One mistake stops it
- 5 complete runs in off and on state are needed
- Outputs in “on” and “off” state
  1. Number of runs needed to achieve 5 correct runs
  2. Time needed to complete those 5 correct runs

Stroop Outputs: The lower the value, the better the performance

Output	Definition	Interpretation
OFFTIME	Time required to complete 5 correct runs in the “Off State”	Psychomotor speed
ONTIME	Time required to complete 5 correct runs in the “On State”	Psychomotor speed and cognitive flexibility
TRIALS OFF	Number of trials it took the subject to get 5 correct runs in “Off state”	Accuracy
TRIALS ON	Number of trials it took the subject to get 5 correct runs in “On state”	Accuracy and flexibility
OFFTIME + ONTIME	Sum of OffTime and OnTime	Composite of psychomotor speed
ONTIME minus OFFTIME	Ontime subtracted by OffTime	Isolated measure of cognitive flexibility

Methods for EncephalApp Validation

- Healthy controls, cirrhotics with prior HE and without prior HE were prospectively recruited
- Patients with active alcohol/illicit drug use, those with active HE (mini-mental<25), inability to give consent and those with red-green color blindness were excluded
- A standard psychometric battery (number connection A/B, Block Design and Digit Symbol tests) was administered
- MHE diagnosis was made according to local norms if ≥2 tests were abnormal after all testing had finished
- Stroop tests were given after the standard battery
  - The “off” state was administered first and then the “on” state
  - 2 training runs were given for each state prior to the recording
  - The tasks were continued in both states until 5 correct runs were achieved

Methods for EncephalApp Validation

- Test-Retest Reliability: A subset of patients and controls were tested twice within 60 days without any underlying change in status
- The following data was collected for in the “off” and the “on” states in the cross-sectional and longitudinal arms
  - Number of runs required to reach 5 correct runs
  - Total time (seconds) for completion of the 5 correct runs
- ROC curves were generated using MHE by standard psychometric tests as the gold standard for the following variables
  - Total time in the “off” state
  - Total time in the “on” state
  - Total Time in “off”+ “on” state
  - Number of runs needed for 5 correct runs in the “off” state
  - Number of runs needed for 5 correct runs in the “on” state

Methods for EncephalApp Validation

- Validation Cohort: A new set of patients with cirrhosis was included to validate the cut-offs set by the original cohort
- Comparison between centers: Between VAMC and VCU Medical Center with respect to results of Stroop tests were also performed

Results

- 125 cirrhotics and 134 age-matched controls were included
- Of the cirrhotics, 82 had not had prior overt HE while the remaining 43 had prior overt HE controlled on lactulose in the majority (32) and lactulose and rifaximin in the remainder.
- 43 additional cirrhotic patients were included in the validation cohort

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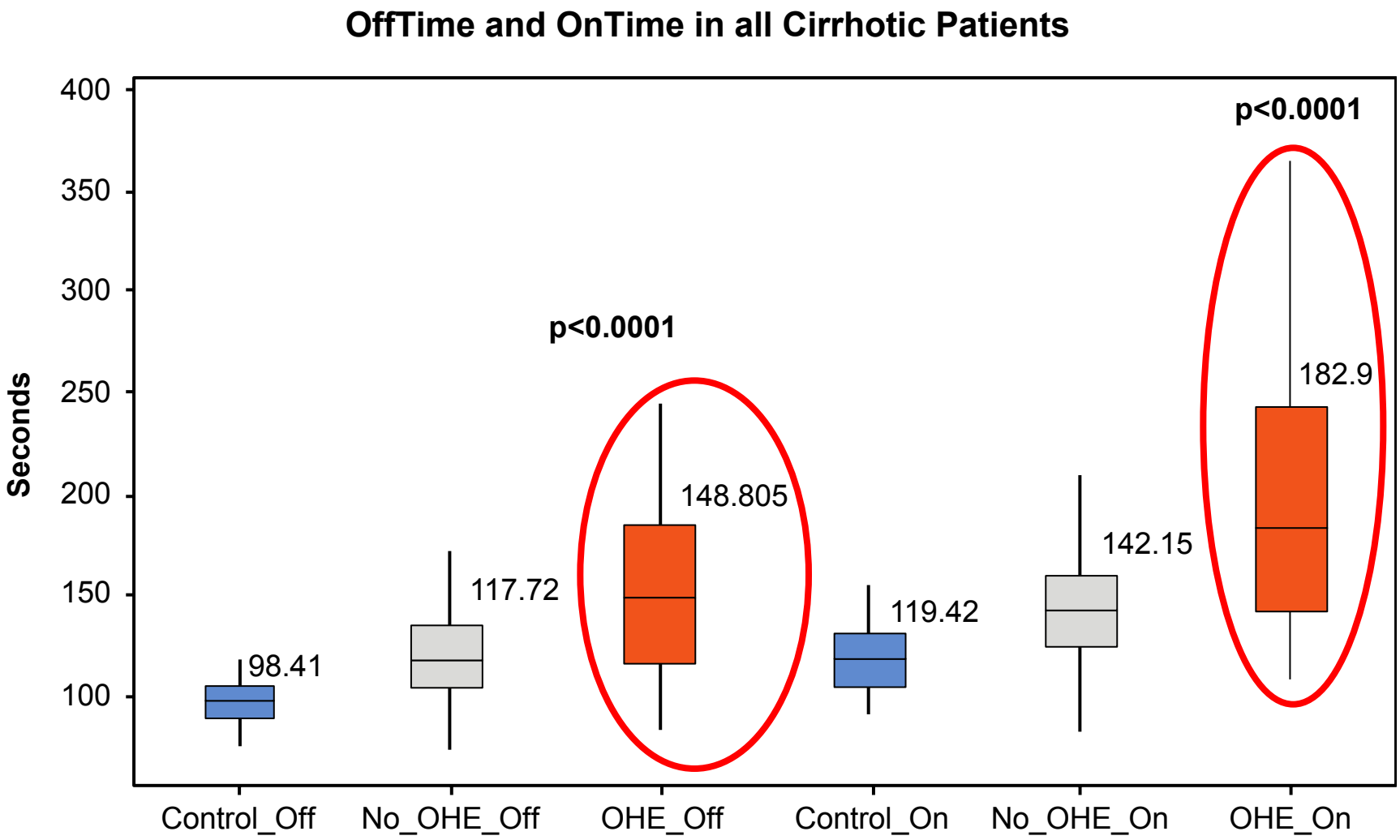
	Healthy Controls (n=51)	Cirrhosis (n=125)	
		No prior OHE (n=82)	With prior OHE (n=43)
Age (years)	55 ± 5	56 ± 6	57 ± 7
MELD score	_	9 ± 3	16 ± 7***
Number connection-A (sec)	27±7	37±19	52±25***
Number connection-B (sec)	69±29	105±77	168±110***
Digit symbol (raw score)	73±11	67±29	94±40***
Block Design (raw score)	36±13	31±15	24±14**
Serial Dotting (sec)	51±12	57±16	45±17***
Line Tracing (seconds)	80±25	100±37	133±71***
Line tracing errors (number)	34±38	37±32	40±33
ICT lures (number)	7±5	10±8	14±8***
ICT targets (% right)	97±6	96±7	89±18***
Weighted Lures (number)	9±7	12±12	23±18***
CHE using standard tests	_	24 (29%)	**31 (72%)*** **
CHE using weighted lures>22	_	15 (18%)	**18 (42%)*** **
CHE using PHES >4 SD	_	44 (54%)	**34 (79%)*** **

Stroop App results	Healthy Controls (n=51)	Cirrhosis (n=125)	
		Without prior OHE (n=82)	With prior OHE (n=43)
Total OffTime (sec)	98±13	121±27	153±40***
Median trials OFF	5 (5-9)	5 (5-19)	6 (5-17)*
Total OnTime (sec)	119±17	148±38	198±63***
Median trials ON	5 (5-13)	6 (5-16)	6 (5-16)*
Ontime minus Offtime(sec)	22±13	27±22	47±37***
Ontime + Offtime(sec)	217±27	271±60	365±98***

Advanced patients have worse App results

	VCU Medical Center (n=62)	VA Medical Center (n=106)
Age (years)	54±7	58±6**
MELD score	10±5	12±6*
Prior OHE (%)	32%	33%
Total OffTime (sec)	117±39	139±45**
Median trials OFF	5 (5-10)	6*** (5-16)
Total OnTime	145±55	173±69***
Median trials OFF	6 (5-23)	6 (5-36)
Ontime minus Offtime(sec)	29±27	35±33
Ontime+Offtime(sec)	262±92	312±112***



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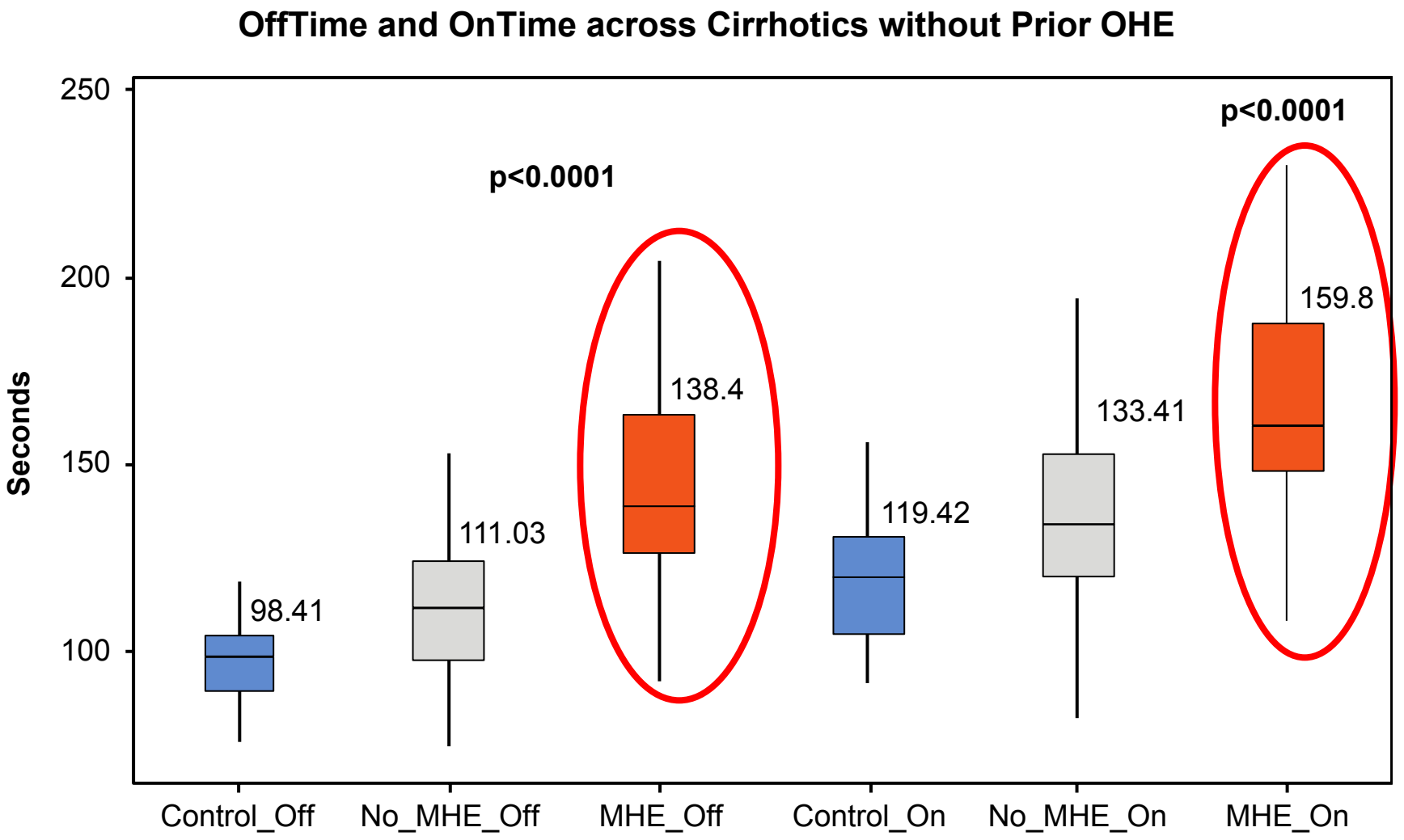

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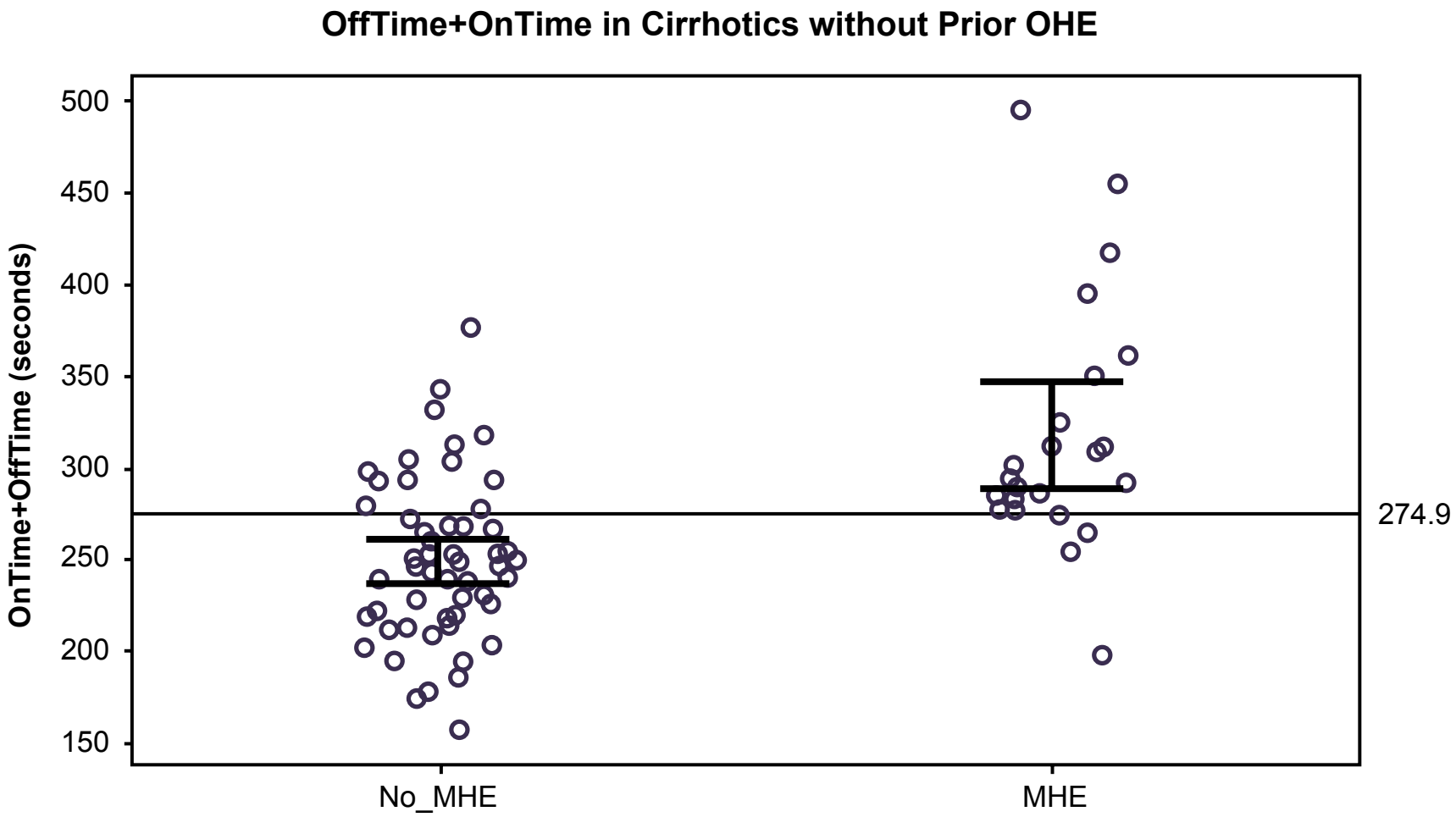

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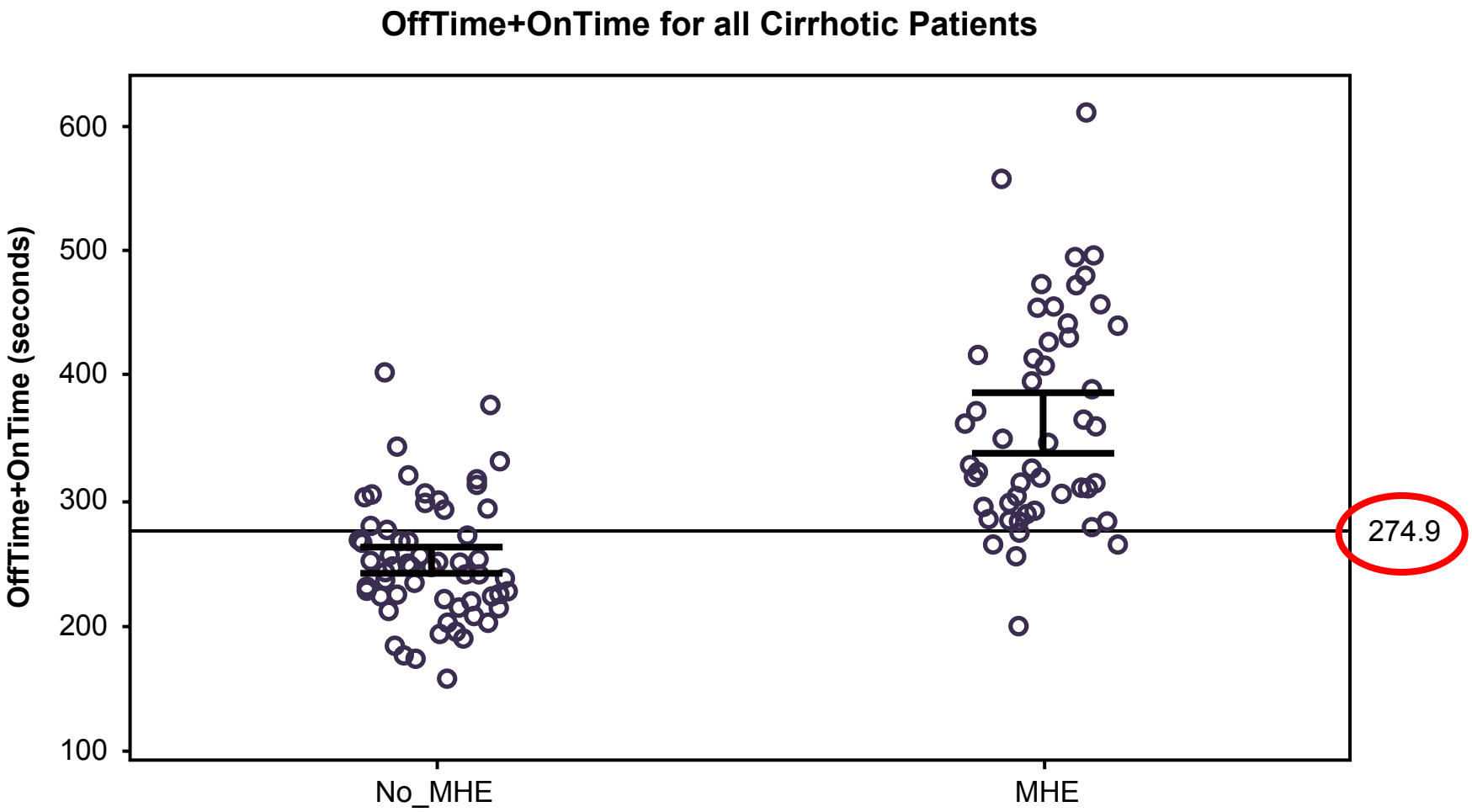

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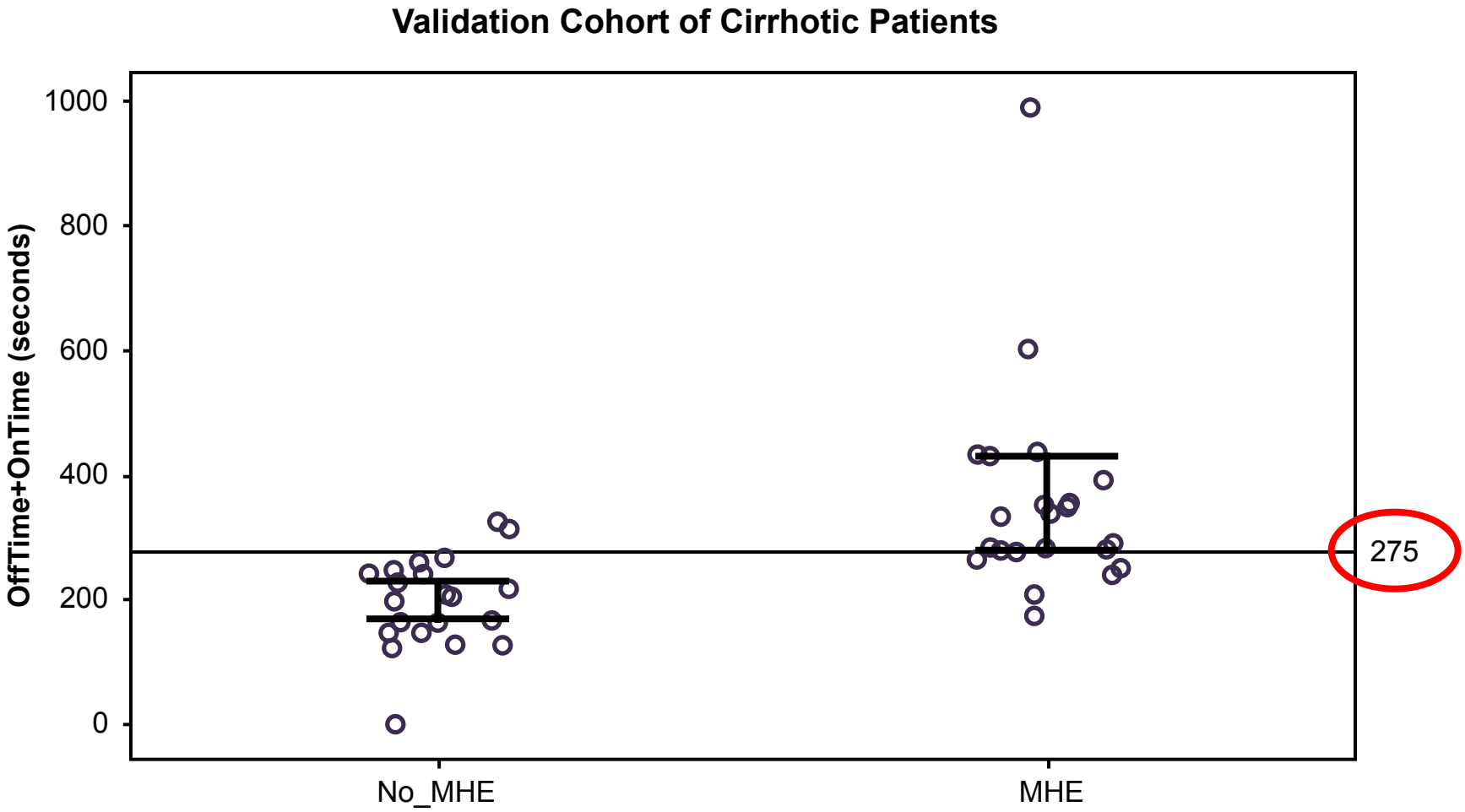

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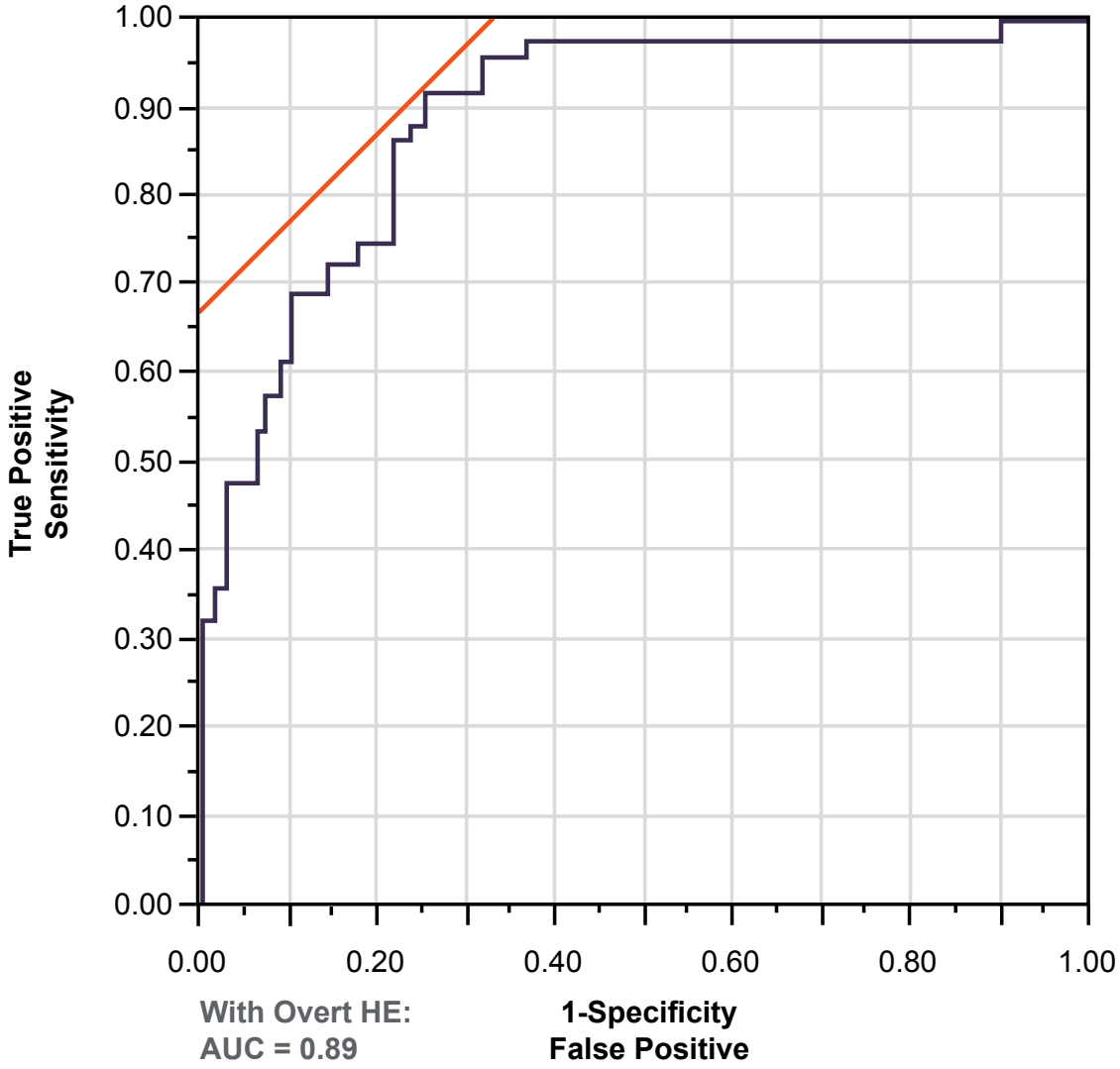
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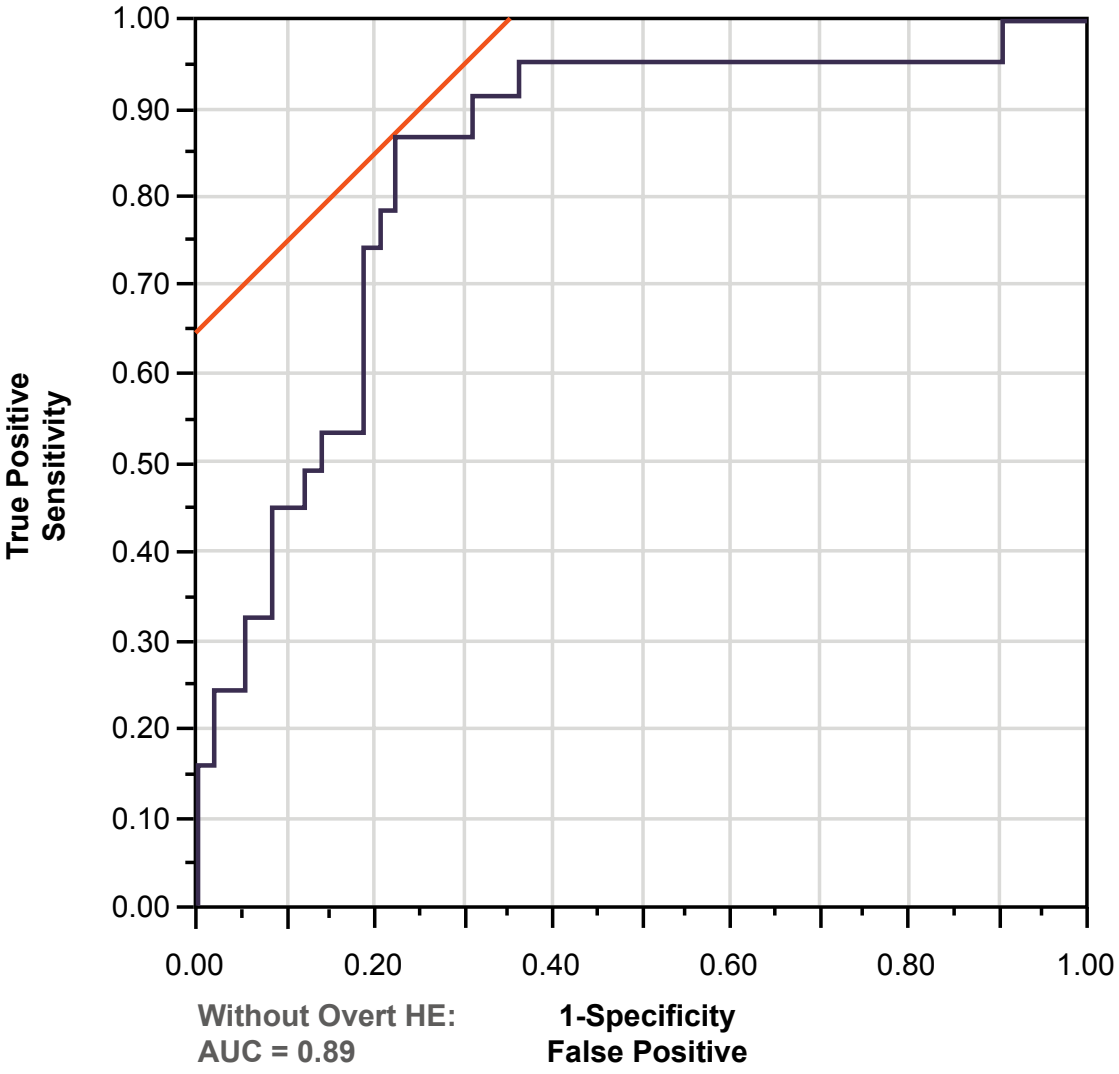
True Positive
Sensitivity
0.00
0.20
0.40
0.60
0.80
1.00
1-Specificity
False Positive
With Overt HE:
AUC = 0.89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True Positive
Sensitivity
0.00
0.20
0.40
0.60
0.80
1.00
1-Specificity
False Positive
Without Overt HE:
AUC = 0.89

Test-retest reliability

- 30 cirrhotic patients (21 without prior OHE and 9 with prior OHE) and 10 controls underwent Stroop evaluation 40±34 days apart

Controls	Baseline	Second test
Time “off”	73 ± 11	68 ± 12
Time “on”	59 ± 7	59 ± 7

Cirrhotic without OHE	Baseline	Second test
Time “off”	70 ± 12	70 ± 9
Time “on”	89 ± 13	84 ± 12*

Cirrhotic with prior OHE	Baseline	Second test
Time “off”	84 ± 20	81 ± 20
Time “on”	108 ± 46	91 ± 29.094

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Practical aspects of covert HE testing and the potential role of the EncephalApp in the overall testing strategy

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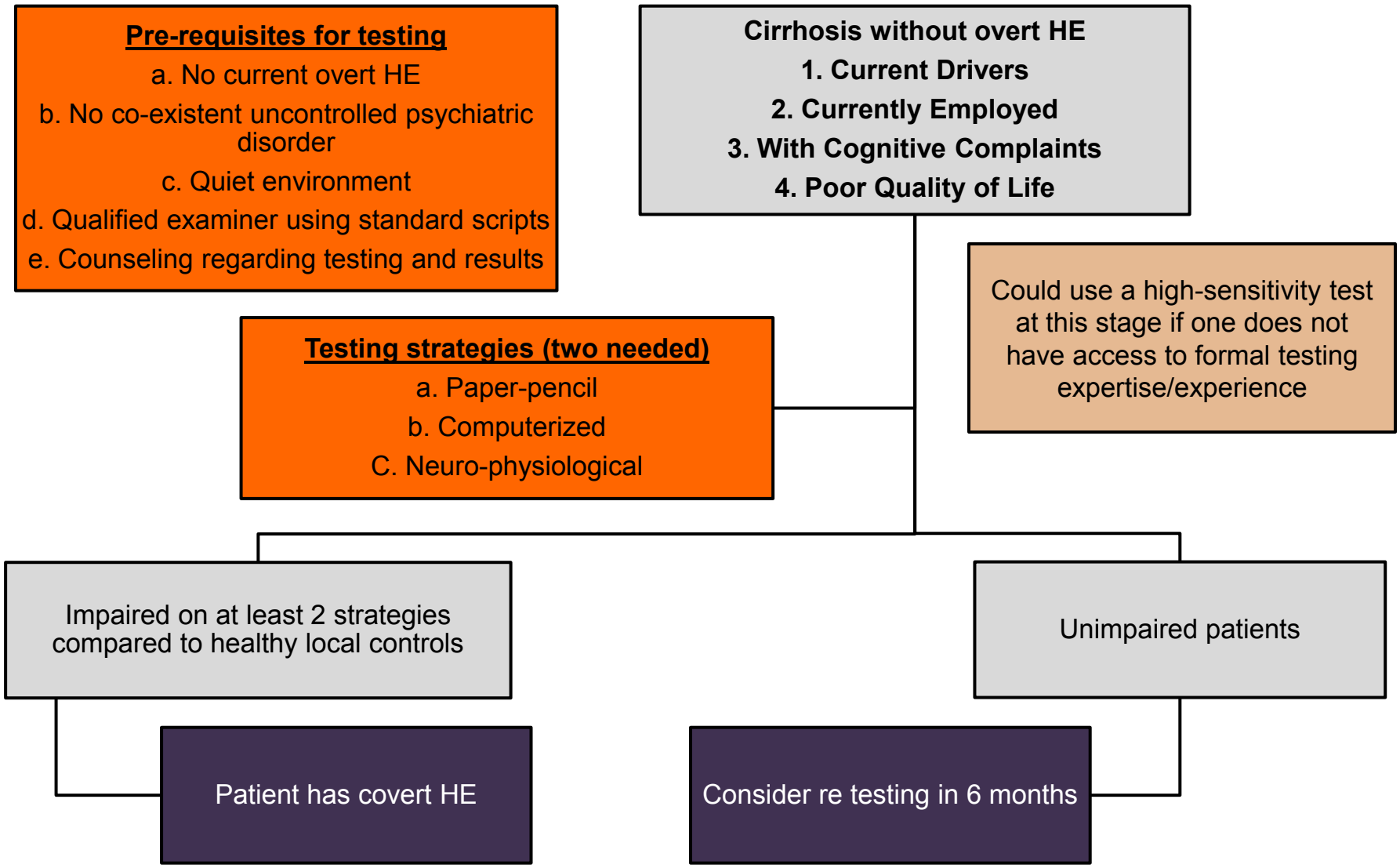
Who should be tested or covert HE?

- Current Drivers
- Currently Employed
- With specific cognitive complaints
- Those with poor quality of life

Kappus et al Clin Gastro Hep 2012

Checklist Pertaining to Covert HE testing

	Yes	No
Pre-testing Checklist		
Patients who are at risk for accidents or job-related mistakes, have cognitive complaints or poor quality of life		
No current overt HE (alert, oriented, MMSE >25)*		
Not on psycho-active drugs (chronic anti-depressants are acceptable)		
No uncontrolled neuro-psychiatric disorders		
Patient is able to comprehend cognitive test procedures		
Adequate vision (corrected with spectacles), hearing and motor strength to perform tasks		
Counseled patient and relatives regarding potential results		
Testing Techniques and Environment		
Quiet environment with relaxed patients		
Using techniques with locally available normative values		
Trained examiner using tests with scripts or protocols		
Post-Testing Questions		
Counseled patient and relatives regarding results and performance		
Offered treatment trial if requested		


Pre-requisites for testing
a. No current overt HE
b. No co-existent uncontrolled psychiatric disorder
c. Quiet environment
d. Qualified examiner using standard scripts
e. Counseling regarding testing and results
Cirrhosis without overt HE
1. Current Drivers
2. Currently Employed
3. With Cognitive Complaints
4. Poor Quality of Life
Could use a high-sensitivity test at this stage if one does not have access to formal testing expertise/experience
Testing strategies (two needed)
a. Paper-pencil
b. Computerized
C. Neuro-physiological
Impaired on at least 2 strategies compared to healthy local controls
Unimpaired patients
Patient has covert HE
Consider re testing in 6 months

Conclusions

- The Stroop smartphone app has good discriminative validity, i.e. performance is worse in prior overt HE patients and in those with MHE diagnosed using the gold standard.
- The Stroop app has good test-retest reliability
- It is easy to perform and administer and within 5 minutes is able to give >88% sensitivity for the diagnosis of MHE and cognitive dysfunction in cirrhosis
- Further validation with the new app in different populations is underway