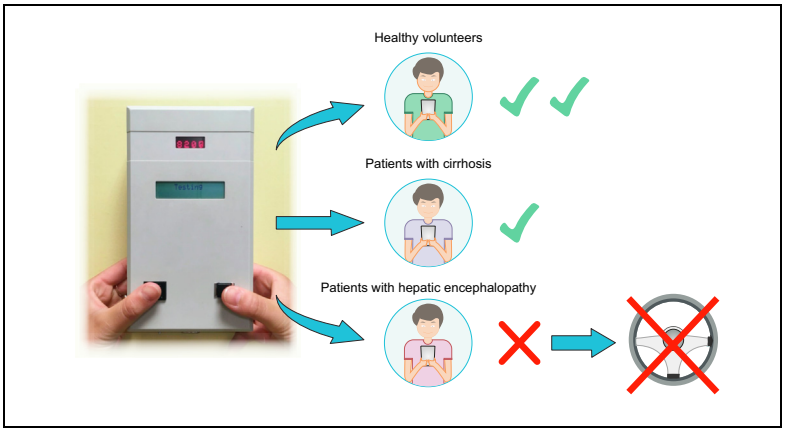
Research Article
Cirrhosis

JOURNAL
OF HEPATOLOGY

The psychomotor vigilance task: Role in the diagnosis of hepatic encephalopathy and relationship with driving ability

Graphical abstract



Highlights

- The Psychomotor Vigilance Task (PVT) is a test of vigilance and provides a series of parameters which are stable in the healthy population, regardless of sex, age and level of education.
- PVT parameters correlate well with standard measures of hepatic encephalopathy (HE).
- PVT parameters may be useful to quantify mild overt HE and identify dangerous drivers among patients with cirrhosis.

Authors

Chiara Formentin, Michele De Rui, Mirko Zoncapè, ..., Paolo Angeli, Piero Amodio, Sara Montagnese

Correspondence

sara.montagnese@unipd.it
(S. Montagnese)

Lay summary

Hepatic encephalopathy (HE) is a complication of advanced liver disease that can manifest as excessive sleepiness. Some patients with HE have been shown to have difficulty driving. Herein, we used a test called the Psychomotor Vigilance Task (PVT), which measures sleepiness and can also be used to assess driving competence. We showed that PVT performance is fairly stable in healthy individuals. We also showed that PVT performance parallels performance in tests which are commonly used in cirrhotic patients to measure HE. We suggest that this test is helpful in quantifying HE and identifying dangerous drivers among patients with cirrhosis.

http://dx.doi.org/10.1016/j.jhep.2018.12.031
 J. Hepatol. 2019, 70, 648–657

Research Article
Cirrhosis

JOURNAL OF HEPATOLOGY

The psychomotor vigilance task: Role in the diagnosis of hepatic encephalopathy and relationship with driving ability

Chiara Formentin[1], Michele De Rui[1], Mirko Zoncapè[1], Silvia Ceccato[1], Lisa Zarantonello[1], Marco Senzolo[2], Patrizia Burra[2], Paolo Angeli[1], Piero Amodio[1], Sara Montagnese[1,*]

[1]*Department of Medicine, University of Padova, Padova, Italy;* [2]*Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy*

See Editorial, pages 590–592

Background & Aims: Hepatic encephalopathy (HE) is a syndrome of decreased vigilance and has been associated with impaired driving ability. The aim of this study was to evaluate the psychomotor vigilance task (PVT), which is used to assess both vigilance and driving ability, in a group of patients with cirrhosis and varying degrees of HE.

Methods: A total of 145 patients (120 males, 59 ± 10 years, model for end-stage liver disease [MELD] score 13 ± 5) underwent the PVT; a subgroup of 117 completed a driving questionnaire and a subgroup of 106 underwent the psychometric hepatic encephalopathy score (PHES) and an electroencephalogram (EEG), based on which, plus a clinical evaluation, they were classed as being unimpaired (n = 51), or as having minimal (n = 35), or mild overt HE (n = 20). All patients were followed up for an average of 13 ± 5 months in relation to the occurrence of accidents and/or traffic offences, HE-related hospitalisations and death. Sixty-six healthy volunteers evenly distributed by sex, age and education served as a reference cohort for the PVT.

Results: Patients showed worse PVT performance compared with healthy volunteers, and PVT indices significantly correlated with MELD, ammonia levels, PHES and the EEG results. Significant associations were observed between neuropsychiatric performance/PVT indices and licence/driving status. PVT, PHES and EEG results all predicted HE-related hospitalisations and/or death over the follow-up period; none predicted accidents or traffic offences. However, individuals with the slowest reaction times and most lapses on the PVT were often not driving despite having a licence. When patients who had stopped driving for HE-related reasons (n = 6) were modelled as having an accident or fine over the subsequent 6 and 12 months, PVT was a predictor of accidents and traffic offences, even after correction for MELD and age.

Conclusions: The PVT is worthy of further study for the purposes of both HE and driving ability assessment.

Lay summary: Hepatic encephalopathy (HE) is a complication of advanced liver disease that can manifest as excessive sleepiness. Some patients with HE have been shown to have difficulty driving. Herein, we used a test called the Psychomotor Vigilance Task (PVT), which measures sleepiness and can also be used to assess driving competence. We showed that PVT performance is fairly stable in healthy individuals. We also showed that PVT performance parallels performance in tests which are commonly used in cirrhotic patients to measure HE. We suggest that this test is helpful in quantifying HE and identifying dangerous drivers among patients with cirrhosis.

Introduction

Patients with hepatic encephalopathy (HE) exhibit psychomotor slowing and impairment of visuomotor coordination, inhibition and executive function, which can negatively impact on their fitness to drive. In 1995 Watanabe *et al.* found that 31% of patients with cirrhosis and 44% of patients with HE were unfit to drive based on their neuropsychological profiles.[1] Bajaj *et al.* recently conducted a cost-effectiveness analysis to assess the benefits of different strategies of minimal HE diagnosis and treatment for reducing accident-related costs, concluding that diagnosis by the inhibitory control test (ICT) and subsequent treatment with lactulose was the most cost-effective approach, with a significant, potential reduction in societal costs by prevented accidents.[2] In a standardised on-road driving test carried out by Wein *et al.*, a professional driving instructor assessed driving performance in 14 patients with minimal HE and 34 unimpaired patients with cirrhosis. The number of times the instructor had to intervene to avoid accidents was nearly 10 times higher in patients with minimal HE compared with unimpaired patients and controls.[3] Kircheis *et al.* studied healthy controls and patients with cirrhosis with and without HE by a real driving test (multiple sensor and camera-equipped car), laboratory, in-car computerised psychometry, and a driving instructor's assessment. Patients with HE showed significantly worse performances compared with healthy controls and unimpaired patients. Moreover, they tended to overestimate their driving abilities.[4] In relation to this, Bajaj *et al.* were able to demonstrate some degree of improvement in self-assessment in patients with minimal HE who underwent driving simulation, including both testing and navigation tasks.[5]

Keywords: Hepatic encephalopathy; Psychomotor Vigilance Task; Driving; Cirrhosis.
Received 17 September 2018; received in revised form 14 December 2018; accepted 16 December 2018; available online 8 January 2019

* Corresponding author. Address: Dipartimento di Medicina, Via Giustiniani, 2, 35128 Padova, Italy. Tel.: +39 049 8218675.
E-mail address: sara.montagnese@unipd.it (S. Montagnese).

The strong relationship between HE and excessive daytime sleepiness has led to the interpretation of HE as a reduced vigilance syndrome,[6] with both diagnostic and therapeutic implications. These include the possibility of diagnosing and quantifying HE using tools that were first developed for the evaluation of sleepiness. One such tool is the psychomotor vigilance task (PVT), a sustained-attention, visual reaction time task that has been widely used both in sleep medicine and the assessment of fitness to drive.[7–18] The PVT is a test of vigilance (*i.e.* the ability to maintain attention focused over a prolonged period of time).[19] The PVT is in fact one of the most widely used measures of vigilance, because of its simple use and the absence of bias related to familiarity with the task[20] or to acquired skills, such as education or aptitude. Its sensitivity has been tested in several conditions of total or partial sleep deprivation, both in different categories of patients and in healthy individuals.[21,22] The PVT has also been used to assess sleepiness and predict sleepiness-related road traffic accidents in occupational clinics, particularly within the context of obstructive sleep apnoea.[15] By contrast, out of computerised tests used so for minimal/covert HE diagnosis: (i) The ICT is a computerised test of response inhibition and working memory.[23] It has been judged to have good validity but requires highly functional patients. (ii) The Stroop test evaluates psychomotor speed and cognitive flexibility by the interference between recognition reaction time to a coloured field and a written colour name;[24,25] again, this is a complex task that is only applicable in highly functional patients. (iii) The SCAN Test is a computerised test that measures speed and accuracy to perform a digit recognition memory task of increasing complexity,[26,27] mostly exploring working memory. (iv) The continuous reaction time (CRT) test relies on repeated registration of the motor reaction time (pressing a button) to auditory stimuli (through headphones). The most important test result is the CRT index, which measures the stability of the reaction times. Age and sex appear to exert limited influence and there are no learning and/or tiring effects.[28,29] This test, which has been used mostly in Denmark, is the only one that is similar to the PVT.

Therefore, the aim of the present study was threefold: (i) to obtain PVT Italian reference data by administering the test to a group of healthy volunteers of varying age, sex and educational attainment; (ii) to study the relationship between PVT indices and accepted, standard neuropsychological and neurophysiological HE measures; and (iii) to analyse the relationship between PVT indices and driving performance and to evaluate the prognostic value of the PVT in terms of risk of road traffic accidents and traffic offences.

Patients and methods

In total, 145 consecutive in- and outpatients with cirrhosis (120 males, age ± SD: 59 ± 10 years) referred to our HE clinic were enrolled. The diagnosis of cirrhosis was clinical, biochemical, radiological and, where necessary, histological. The severity of hepatic failure was based on the Child-Pugh[30] and model of end-stage liver disease (MELD)[31] scores. Exclusion criteria were: overt HE grades II (with spatiotemporal disorientation), III and IV;[32,33] significant neurological comorbidity or head injury; cognitive disorders related to other metabolic diseases; cardiovascular diseases; treatment with psychoactive drugs; or shift work over the preceding 5 years. A convenience sample of 66 healthy volunteers (35 males, 58 ± 12 years) recruited to cover both sexes, all relevant decades of age and all main levels of educational attainment served as a reference for the PVT indices; none of the volunteers was taking chronic medication or had been a shift-worker over the preceding 5 years.

Standard hepatic encephalopathy assessment

All patients underwent a clinical neuropsychiatric assessment to establish the presence of mild overt HE (grade I or grade II, diagnosed because of the presence of flapping tremor in the absence of spatiotemporal disorientation);[32,33] in addition, 106 patients underwent formal neuropsychological and neurophysiological evaluation.

Neuropsychological performance was assessed using the Number Connection Tests A and B, the Digit Symbol test, the Line Tracing test, and the Serial Dotting test.[34] Results were scored in relation to age-adjusted and education-adjusted Italian norms.[35] Performance was classified as impaired if the sum of the standard deviations for the individual tests, referred to as the psychometric hepatic encephalopathy score (PHES), was ≤−4;[34,35] the mean of the z-scores for each subtest (MPZS)[35] was also used for purposes of correlation analysis.

A wake electroencephalogram (EEG) was recorded for 10 min, with eyes closed, in a condition of relaxed wakefulness, using a 21-electrode EEG cap. One continuous 80–100 s period of artefact-free EEG tracing was selected for subsequent spectral analysis by fast Fourier transform. The following spectral parameters were calculated on the P3–P4 derivation: the mean dominant frequency, which is an estimate of the background frequency of the EEG; and the relative power of the spectral bands delta (1–3.5 Hz), theta (4–8 Hz), alpha (8.5–13 Hz) and beta (13.5–25.5 Hz). EEGs were classified as normal or abnormal based on the spectral criteria proposed by Van der Rijt *et al.*[36] and subsequently modified by Amodio *et al.*[37]

Neuropsychiatric status was classified as unimpaired (*i.e.* no clinical evidence of overt HE according to the West-Haven criteria[32] and both normal PHES and normal EEG; n = 51), minimal HE (*i.e.* no overt HE but abnormal PHES and/or EEG; n = 35), and mild overt HE (n = 20). Of the 20 patients with mild overt HE, 16 were West-Haven grade I and 4 were West-Haven grade II, diagnosed based on the presence of flapping tremor.[32,33] Thus, none of these patients were obviously disorientated for space and/or time, and none had gross neurological or psychiatric alterations. All proved capable of undergoing the full neuropsychiatric evaluation (*vide infra*).

Psychomotor vigilance task

All patients underwent the PVT. The PVT administration equipment, a small box which can be held with two hands (Fig. 1), is provided with a screen on which a series of consecutive numbers appear (which actually represent a count in ms), and 2 buttons (bottom of the box). Participants are asked to press the button (the left one if they are left-handed, the right one if they are right-handed) as soon as the number appears on the screen. Each PVT administration lasts ∼10 min, during which the stimuli appear at random intervals, which vary between 2 s and 10 s. A 1-min practice run is performed before the actual test. Data are then analysed with the PVTCommW (version: 2.13.1.0; ©1999, Ambulatory Monitoring, Inc.) and React (REACT – Data Analysis for the PVT-192; version: 1.1.05; ©1999, Ambulatory Monitoring, Inc.) software.

Fig. 1. The hand-held psychomotor vigilance task administration equipment. Size, screen on which the stimuli appear (blue arrow) and response buttons for right/left-handed individuals (red boxes) are indicated.

The main indices obtained are: (i) Good R's (the absolute number of correctly answered stimuli); (ii) mean reaction time, median reaction time and standard deviation (SD) reaction time; (iii) minimum/maximum reaction time (the fastest/slowest reaction times, respectively); (iv) lapses (the number of times the reaction time is >500 ms); (v) lap (SQR XFRM), which is the transformed square root of the lapses, obtained from the equation $[\sqrt{((\text{Lapses}))} + \sqrt{((\text{Lapses} + 1))}]$; (vi) total number of errors, including false responses (reaction time <100 ms), false starts, wrong button (Wrong key R's), button pressed for more than 3 s (Key Held > 3 s) and number of stimuli not followed by a response for more than 30 s (No R for 30 s); (vii) non-parametric distribution asymmetry [Distrib. Asym.; a measure of the 'skewness' of the reaction time distribution, derived from the equation (mean–median)/SD]; (viii) mean F reaction time and SD F reaction time (mean and SD of the 10% fastest reaction times); and (ix) mean S reaction time and SD S reaction time (mean and SD of the 10% slowest reaction time). The mean, median, minimum and maximum reaction times, the number of lapses and the total number of errors were utilised as an overall summary set of indices of PVT performance.

Driving/licence status

On recruitment, 117 patients completed a questionnaire about their driving performance, with the aim of collecting data on whether they were in possession of a driving licence, and, if not, reasons for its absence and/or suspension; the type of vehicle they drove, habitual routes (urban, extra-urban, highway, or miscellaneous) and the number of kilometres driven per week; and whether they had committed traffic offences and/or had been involved in road traffic accidents during the previous year.

Follow-up

Patients were followed up for an average of 13 ± 5 months from the date of evaluation, recording the following data at both 6 and 12 months: whether they were dead or alive, had had episodes of HE requiring hospitalisation, had committed traffic offences (except for parking offences) and/or had been involved in road traffic accidents.

Ethics

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (European Guidelines). The protocol was submitted to, and approved by, the local Ethics Committee. All participating subjects provided written, informed consent.

Statistical analysis

Results are expressed as mean ± SD, unless otherwise specified. Normality was tested for by the Shapiro–Wilks test. Differences between groups were tested by the Student *t* test and/or Mann–Whitney *U* test or ANOVA/Kruskal-Wallis ANOVA (*post hoc*: Tukey and/or multiple comparisons of mean ranks). Associations were tested by the Pearson X^2. Correlations were tested by the Pearson r/Spearman R, as appropriate. Kaplan-Meier analysis (*post hoc*: Cox–Mantel test) was used to evaluate the predictive ability of PVT (upper *vs.* all other quartiles within the patient population), EEG (normal *vs.* abnormal according to standard thresholds) and PHES (normal *vs.* abnormal according to Italian normative data) in relation to HE-related hospitalisations, survival and road traffic accidents. A Cox proportional hazards model was used to evaluate the predictive ability of PVT parameters as continuous variables, taking into account age, MELD and, where appropriate, standard HE measures. Finally, 3 additional Cox proportional hazards models were used to evaluate the predictive ability of PVT parameters by also making use of the group of patients who did not drive despite being in possession of a driving licence. These were treated as if: (i) they would all have an accident and/or fine over the subsequent 6 or 12 months; (ii) half, selected at random, would have an accident and/or fine over the subsequent 6 and 12 months; and (iii) those who provided reasons that were related to HE for not driving despite having a licence (n = 6) would have an accident and/or fine over the subsequent 6 and 12 months. In all 3 instances, the accident and/or fine dates were placed at 3 and 6 months for the 6- and 12-month follow-up periods, respectively (*i.e.* in the middle of the follow-up period).

Results

Demographic and laboratory features of healthy volunteers and patients with cirrhosis are presented in Table 1. Age was comparable in the 2 groups; patients were more commonly males. Both a history of overt HE and ammonia-lowering treatment were prevalent in the patient population (most likely because the study was conducted in a tertiary referral centre for hepatology) and increased in parallel with worsening neuropsychiatric status. Overall, patients with a positive HE history had worse PHES (MPZS: −0.74 ± 1.24 *vs.* −0.04 ± 0.85, $p < 0.01$), worse EEG (MDF in Hz: 9.2 ± 2.0 *vs.* 10.2 ± 1.9, $p < 0.05$) and PVT (lapses: 12 ± 17 *vs.* 6 ± 2, $p < 0.05$) performances, and worse liver failure (MELD 14.3 ± 5.3 *vs.* 11.6 ± 4.1, $p < 0.05$) compared with their counterparts with

Table 1. Demographic and hepatic failure indices in healthy volunteers and patients with cirrhosis, by degree of neuropsychiatric impairment.

	Healthy volunteers (n = 66)	All patients (n = 145)	Unimpaired (n = 51)	MHE (n = 35)	OHE (n = 20)
Age (mean ± SD)	58 ± 12	59 ± 11	58 ± 12	58 ± 9	62 ± 11
Sex M/F (n)	35/31[a]	120/25[a]	46/7	29/7	20/1
Aetiology of cirrhosis (%):	–				
Viral		32	38	34	20
Alcohol		33	35	26	25
Viral + alcohol		13	13	17	10
Metabolic		6	4	9	15
Other causes		16	10	14	30
Child A/B/C (%)	–	42/41/17	69/22/9	24/48/28	13/62/25
MELD/MELD-Na (mean ± SD)	–	13 ± 5/15 ± 6	11 ± 4/13 ± 5	15 ± 5/17 ± 6	15 ± 5/16 ± 5
Fasting venous ammonia (mMol/L)[b]	–	56 ± 35	44 ± 29	67 ± 39	66 ± 37
Ammonia-lowering treatment (%)	–	71	51	71	75
OHE history (%)	–	56	43	56	90

HE, hepatic encephalopathy; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy.
[a] p <0.0001.
[b] Data available for 63 patients in total, 29 unimpaired patients, 21 with MHE and 9 with OHE.

Table 2. Main PVT indices in healthy volunteers, by decade of age, sex, and educational attainment.

	Decade of age	Mean RT (ms)	Median RT (ms)	Min RT (ms)	Max RT (ms)	Lapses (n)	Total errors (n)
Age (years)	20–29 (n = 36)	257 ± 25	245 ± 24	181 ± 19	483 ± 143	0.56 ± 0.78	0.89 ± 1.64
	30–39 (n = 18)	250 ± 28	239 ± 30	179 ± 16	471 ± 108	0.33 ± 0.68	1.61 ± 2.45
	40–49 (n = 22)	265 ± 34	252 ± 32	186 ± 20	548 ± 170	1.05 ± 1.62	1.00 ± 1.41
	50–59 (n = 23)	263 ± 41	248 ± 37	187 ± 29	556 ± 244	1.13 ± 1.71	1.61 ± 2.06
	60–69 (n = 10)	283 ± 47	266 ± 45	193 ± 22	812 ± 644	2.1 ± 1.91	1.10 ± 1.10
	70–79 (n = 5)	496 ± 223[a,b,c,d,g]	460 ± 215[a,b,c,d,f]	289 ± 95[a,b,c,d,e]	1,506 ± 839[a,b,c,d,f]	33.2 ± 38.58[a,b,c,d,g]	0.20 ± 0.45
	80–89 (n = 6)	582 ± 301[a,b,c,d,g]	537 ± 311[a,b,c,d,s]	336 ± 182[a,b,c,d,g]	1,706 ± 555[a,b,c,d,g]	37.33 ± 31.14[a,b,c,d,g]	0.00 ± 0.00
Sex	Males (n = 54)	284 ± 131	268 ± 130	194 ± 72	649 ± 418	3.70 ± 12.24	1.50 ± 1.88 [h]
	Females (n = 48)	301 ± 117	284 ± 104	204 ± 54	684 ± 533	5.75 ± 17.67	0.73 ± 1.57
Education (years)	5–7 (n = 39)	284 ± 147	272 ± 148	198 ± 83	538 ± 254	3.03 ± 13.88	1.28 ± 2.03
	8–12 (n = 12)	261 ± 26	248 ± 23	185 ± 18	535 ± 203	0.75 ± 1.14	1.00 ± 1.91
	13–16 (n = 12)	253 ± 25	241 ± 22	175 ± 20	472 ± 121	0.67 ± 1.23	1.42 ± 2.39
	≥17 (n = 4)	285 ± 56	269 ± 49	191 ± 32	616 ± 152	3.75 ± 5.56	0.50 ± 0.58
	≥17 (n = 3)[i]	257 ± 4	244 ± 5	175 ± 0	586 ± 171	1.00 ± 1.00	0.67 ± 0.60

Max, maximum; Min, minimum; PVT, psychomotor vigilance task; RT, reaction time.
[a] p <0.001 *vs.* decade 20–29; [b] p <0.001 *vs.* decade 30–39; [c] p <0.001 *vs.* decade 40–49; [d] p <0.001 *vs.* decade 50–59; [e] p <0.05 *vs.* decade 60–69; [f] p <0.01 *vs.* decade 60–69; [g] p <0.001 *vs.* decade 60–69; [h] p <0.05 males *vs.* females; [i] Excluding the 83-year old male within the group.

no HE history, which is expected. Similarly, treated patients had worse PHES, EEG and PVT performances (also when compared within HE classes), and a trend towards worse liver function (MELD 13.8 ± 4.7 *vs.* 11.7 ± 6.1, $0.05 < p < 0.1$; Pugh 7.8 ± 1.9 *vs.* 6.8 ± 2.2, $0.05 < p < 0.1$) compared with their untreated counterparts, which is also expected.

Age, sex and level of education (Table 2) had limited or no effect on PVT indices in the healthy population, with age being associated with significantly slower reaction times and more lapses only when above 70 years. Males and females had comparable reaction times, whereas males showed significantly more total errors (Table 2). Educational attainment, split by primary (5–7 years of education), middle school (8–12), high school (13–16) and university (≥17), had no effect on PVT indices. The results within the very small group of patients with a university education was skewed by the fact that 1 individual in the group was the oldest recruited healthy volunteer (83 years of age; Table 2).

As a group, patients showed worse PVT performance compared with healthy volunteers, with slower reaction times (*i.e.* mean reaction time: 404 ± 458 *vs.* 313 ± 150 ms, $p < 0.001$; maximum reaction time: 1528 ± 3136 *vs.* 769 ± 556 ms, $p < 0.01$) and a higher number of lapses (9.2 ± 14.7 *vs.* 7.0 ± 18.3, $p < 0.05$).

Psychomotor vigilance task *vs.* standard hepatic encephalopathy indices

A significant correlation was observed between the number of lapses on PVT and the degree of hepatic failure (MELD score; $p < 0.05$). PVT indices were comparable in patients with alcohol-related cirrhosis *vs.* other aetiologies. Patients with mild overt HE showed significantly longer reaction times and a higher number of lapses compared with both patients with minimal HE and unimpaired patients ($p < 0.001$ on all indices except for the median reaction time). Differences between patients with minimal HE and unimpaired patients were not significant. PVT indices were significantly worse in patients with abnormal *vs.* normal EEG (all indices except maximum reaction time and total errors), and patients with abnormal *vs.* normal PHES performance (all indices except total errors) (Table 3). Significant correlations were observed between PVT indices and fasting venous ammonia levels (median reaction time: R = 0.29, $p < 0.05$; minimum reaction time: R = 0.25, $p < 0.05$).

Neuropsychiatric status and driving performance

Of the 117 patients who completed the driving questionnaire on the day of enrolment, 102 (87%) had a driving licence and 14 (14%) of these did not drive; 2 patients drove despite not having a licence; 86 patients drove a car, 2 a van, 1 a truck and 1 a boat.

Table 3. PVT indices in patients with normal *vs.* abnormal EEG and PHES performance.

	EEG normal (n = 53)	EEG abnormal (n = 53)	PHES normal (n = 75)	PHES abnormal (n = 31)
Mean RT	320 ± 86[a]	507 ± 651[a]	324 ± 98[b]	462 ± 251[b]
Median RT	298 ± 84[a]	405 ± 337[a]	297 ± 62[b]	391 ± 98[b]
Minimum RT	204 ± 31[a]	221 ± 44[a]	205 ± 30[b]	226 ± 45[b]
Maximum RT	1,004 ± 1,043	2,187 ± 4,212	1,027 ± 1,019[b]	2,165 ± 4,158[b]
Lapses	5 ± 11[a]	15 ± 16[a]	5 ± 9[b]	19 ± 16[b]
Total errors	1.4 ± 2.1	2.0 ± 3.5	1.5 ± 2.0	1.5 ± 3.3

EEG, electroencephalogram; PHES, psychometric hepatic encephalopathy score; PVT, psychomotor vigilance task; RT, reaction time.
[a] Normal *vs.* abnormal EEG: p <0.01.
[b] Normal *vs.* abnormal PHES: p <0.01.

Of the 14 patients who did not drive despite having a licence, 10 provided reasons for not driving. In 6 instances, such reasons appeared to relate to HE: 1 patient reported that their hepatologist had suggested they stopped driving; 2 patients had stopped driving after episodes of overt HE because of medical and/or family advice; 1 patient had stopped driving after an accident that was felt to relate to HE; and 2 patients had stopped driving because they felt unsafe. In the remaining 4 cases, reasons appeared to be unrelated to HE: 1 patient reported having not mended the car after it had broken down; 1 reported having lent the car to their son; and 2 patients had stopped driving several years beforehand, while misusing drugs, and had never resumed driving. The average distance driven was 2.2 ± 1.0 km per week. During the previous year, 9 patients (10%) had been fined (6 for speeding and 3 for passing through red lights) and 11 (12%) had been involved in an accident. PHES, EEG and PVT indices were comparable in patients who had or had not been fined or involved in accidents in the previous year (data not shown). The licence and driving status of patients is presented in Fig. 2, by degree of neuropsychiatric impairment (n = 78). Significant associations were observed between licence/driving status and neuropsychiatric performance (X^2 = 19.7; p = 0.003). The likelihood of not driving despite having a licence increased in parallel with the degree of neuropsychiatric impairment (18% of patients in this situation being unimpaired, 27% having minimal HE and 55% mild overt HE). Driving experience was comparable in patients with a licence who did and did not drive (years from obtainment of the

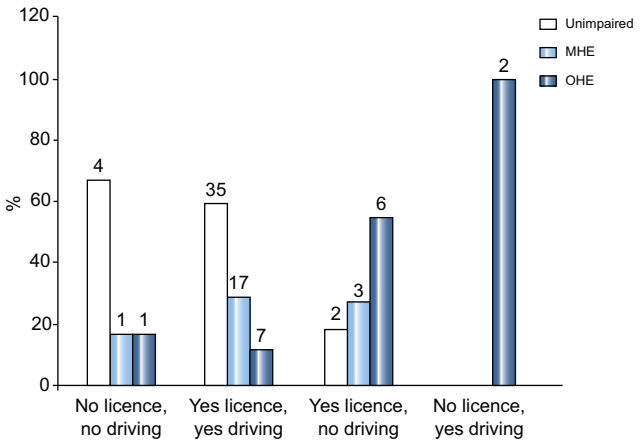


Fig. 2. Licence and/or driving status by degree of neuropsychiatric impairment. Data are expressed as a percentage (X^2 = 19.7; p = 0.003). Absolute patient numbers are indicated on the top of each column. MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy.

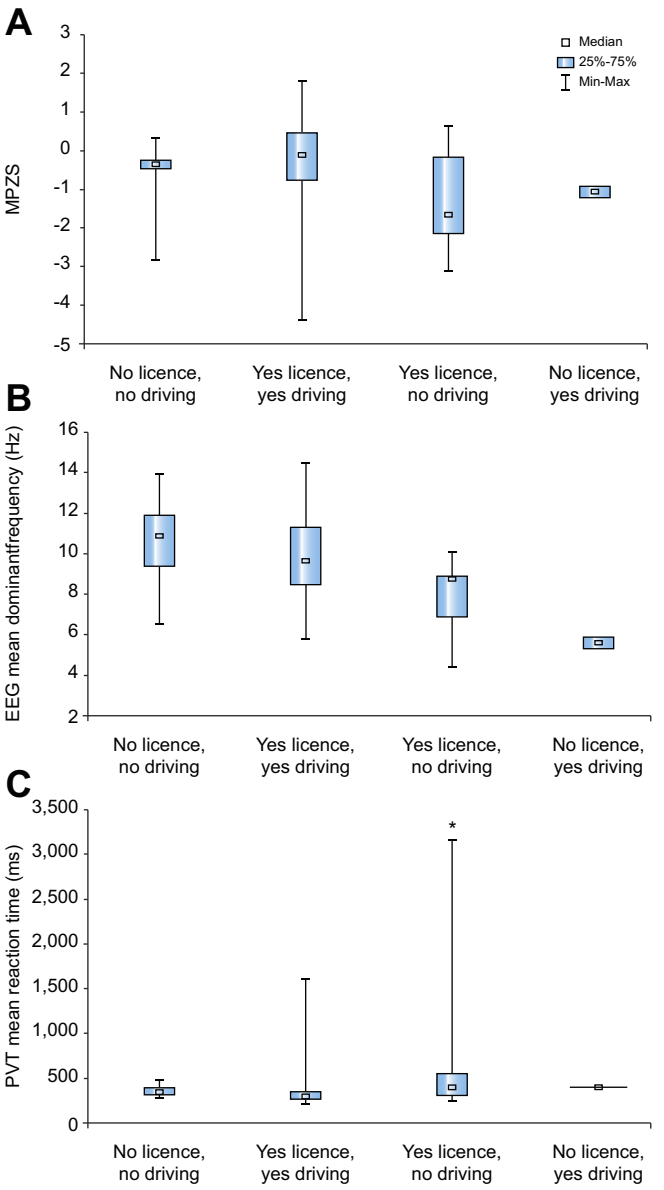


Fig. 3. Neuropsychological, neurophysiological and psychomotor vigilance task (PVT)-derived parameters by licence/driving status. (A) Mean psychometric hepatic encephalopathy z score (MPZS; Kruskal-Wallis ANOVA p = 0.080). (B) Electroencephalogram (EEG) mean dominant frequency (Kruskal-Wallis ANOVA p = 0.018). (C) PVT-derived mean reaction time (Kruskal-Wallis ANOVA p = 0.018). *p < 0.05 on *post hoc* comparison of patients who had a licence and drove, and those who had a licence and did not drive.

licence: 37.3 ± 10.5 *vs.* 37.6 ± 9.6). Both patients driving without a licence had overt HE on the day of study.

Representative PHES, EEG and PVT indices, by licence and driving status, are shown in Fig. 3. Patients were divided into 4 groups in relation to driving habits and possession of a driving licence (4 yes/no combinations). Neuropsychiatric performance (MPZS, Fig. 3A), neurophysiological parameters (EEG mean dominant frequency, Fig. 3B) and the PVT index mean reaction time (Fig. 3C) were compared among the 4 groups. *Post hoc* differences were significant only for the PVT parameter, but available total numbers were higher for the PVT (n = 116) compared with the PHES and EEG (n = 74).

Follow-up (HE-related hospitalisations and survival)

All patients were prospectively followed up for an average of 13 ± 5 months; at 6 months, 11 (8%) patients were dead and 6 (4%) had received a liver transplant; at 12 months, 21 (14%) patients were dead and 9 (6%) had received a liver transplant. Given that all patients who had received a liver transplant had done so because of hepatic failure, they were treated as complete cases (=dead). Twenty-six (19%) patients had an HE-related hospitalisation at 6 months and 32 (24%) at 12 months.

Kaplan-Meier analysis (*post hoc* test: Cox–Mantel) confirmed the predictive ability of the EEG (normal *vs.* abnormal) in relation to HE-related hospitalisations at 6 ($p < 0.01$) and 12 ($p < 0.01$) months. A trend was also detected for PHES (normal *vs.* abnormal; $0.05 < p < 0.1$ at 12 months). By contrast, the EEG did not predict death at 6 or 12 months, whereas PHES did ($p < 0.01$ and $p < 0.05$, respectively).

Both the PVT-derived mean reaction time and lapses (upper quartile *vs.* all others within the patient group) predicted HE-related hospitalisations at 6 months ($p < 0.001$ and $p < 0.001$, respectively; Fig. 4A) and 12 months ($p < 0.001$ in both instances). In addition, the PVT-derived mean reaction time and lapses (upper quartile *vs.* all others within the patient group) also predicted survival at 6 months ($p < 0.05$ and $p < 0.001$, respectively; Fig. 4B) and 12 months ($p < 0.05$ and $p < 0.001$, respectively). When the PVT parameters mean reaction time and lapses, treated as continuous variables, were included in a Cox proportional hazards model together with age and MELD, they remained significant predictors of both HE-related hospitalisations and death at 6 and 12 months (Table 4).

Finally, we also tested a multivariate model including the PVT parameter lapses, MELD, age, PHES, and the continuous EEG parameter MDF. This was both stretched in terms of power and affected by the fact that PHES, EEG and PVT are to some extent redundant because they measure aspects of the same syndrome (Table 3). Nonetheless, when all variables were kept in the model, only EEG and MELD were significant predictors of subsequent HE-related hospitalisations at 6 (only EEG) and 12 (both MELD and EEG) months. When the EEG was removed, thus leaving 2 neuropsychological tests (PHES and PVT) in the model, only PVT lapses and MELD were significant predictors of subsequent HE-related hospitalisations at 6 (both lapses and MELD) and 12 (only MELD) months.

Follow-up (road traffic accidents and traffic offences)

Follow-up information on road traffic accidents and/or traffic offences was available for 74 patients at 6 months and 65 patients at 12 months. At 6 months, 3 patients (out of 74, all in the category of those having a licence and driving) had been fined (all for speeding), and 2 (out of 74, all in the category of those having a licence and driving) had been involved in accidents; in 1 case, the patient had been responsible for the accident. At 12 months, 3 patients (out of 65, all in the category of those having a licence and driving) had been fined (2 for speeding and 1 for driving in the lane reserved for special vehicles) and 2 patients (out of 65, all in the category of those having a licence and driving) had been involved in accidents; in 1 case, the patient had been responsible. Neither continuous nor ordinal PVT, PHES or EEG indices predicted the occurrence of accidents or traffic offences over the follow-up period. However, individuals with compromised PVT, PHES and EEG performances were often not driving, despite being in possession of a licence, having probably been advised not to drive by their family and/or physicians (Fig. 2). When all 14 patients who did not drive were assumed to have had an accident and/or fine over the subsequent 6 and 12 months, lapses were a predictor of outcome, even after correction for MELD and age. When 7 (randomly selected) of the 14 patients who did not drive were assumed to have had an accident and/or fine over the

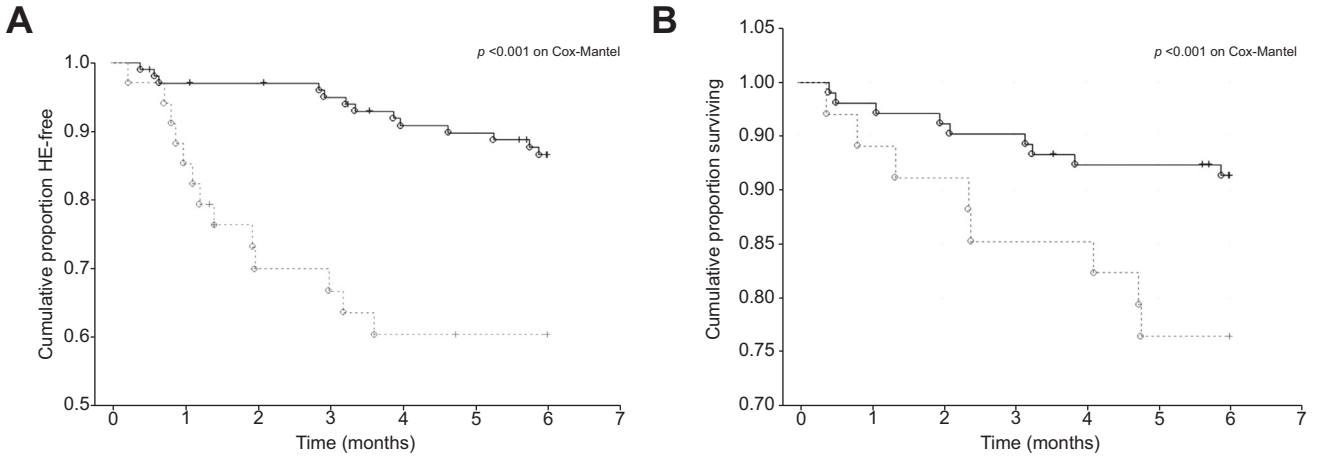


Fig. 4. Cumulative proportion of hepatic encephalopathy (HE)-free (A) and surviving (B) patients at 6 months follow-up, split by upper (grey plot) *vs.* all other quartiles (black plot) of the psychomotor vigilance task-derived mean reaction time. Circles indicate complete cases [HE-related hospitalisations in (A) and deaths in (B)], whereas crosses indicate censored cases.

Table 4. Cox proportional hazards models (age, MELD and PVT parameters) for death and HE-related hospitalisations at 6 and 12 months.

Follow-up			Parameter estimate	SE	*p* value
6 months	Survival	Age	−0.009	0.052	0.859
		MELD	0.110	0.098	0.266
		PVT mean RT	***0.004***	***0.001***	***0.000***
		Age	0.016	0.025	0.530
		MELD	***0.153***	***0.046***	***0.001***
		PVT lapses	***0.032***	***0.012***	***0.007***
	HE	Age	−0.003	0.031	0.931
		MELD	0.061	0.080	0.445
		PVT mean RT	***0.003***	***0.000***	***0.000***
		Age	0.017	0.021	0.417
		MELD	**0.105**	**0.050**	**0.037**
		PVT lapses	**0.024**	**0.011**	**0.028**
12 months	Survival	Age	−0.002	0.031	0.945
		MELD	**0.140**	**0.056**	**0.013**
		PVT mean RT	***0.004***	***0.000***	***0.000***
		Age	0.022	0.020	0.278
		MELD	***0.174***	***0.036***	***0.000***
		PVT lapses	***0.030***	***0.011***	***0.007***
	HE	Age	0.006	0.023	0.801
		MELD	0.083	0.061	0.173
		PVT mean RT	***0.002***	***0.000***	***0.000***
		Age	0.027	0.018	0.143
		MELD	***0.129***	***0.044***	***0.003***
		PVT lapses	0.018	0.011	0.083

Bold typeface: $p < 0.05$. Bold and italic typeface: $p < 0.01$.
HE, hepatic encephalopathy-related hospitalisation; MELD, model for end-stage liver disease; PVT, psychomotor vigilance task; SE, standard error.

subsequent 6 and 12 months, no PVT parameter predicted outcome. When the 6 patients who did not drive for HE-related reasons were assumed to have had an accident and/or fine over the subsequent 6 and 12 months, lapses were a predictor of outcome, even after correction for MELD and age.

Discussion

This was the first study to assess the value of PVT, a test of vigilance that has also been used as a surrogate marker of driving ability,[15,38–46] in patients with cirrhosis and varying degrees of neuropsychiatric impairment. Patients as a group showed worse PVT performance compared with healthy volunteers. PVT indices significantly correlated with both MELD and standard measures of neuropsychiatric performance, such as the paper and pencil battery PHES and the EEG. In addition, PVT indices were particularly compromised in individuals who, despite having a driving licence, did not drive. Finally, PVT indices predicted both HE-related hospitalisations and death over a follow-up period of 6 and 12 months, also after adjustment for age and the degree of hepatic failure.

In the healthy population, the main PVT-derived parameters were affected by age only if over 70, whereas sex and the level of education had little, if any, effect. This is reasonable, given that PVT explores the vigilance domain, is simple, based on a large number of trials, and somewhat comparable to the CRT, which has been shown to have similar features and has also been proposed as a measure of HE.[28] Patients with mild overt HE showed significantly longer reaction times and a higher number of lapses compared with both patients with minimal HE and unimpaired patients, whereas PVT parameters could not distinguish between patients with minimal HE, as diagnosed by PHES and/or EEG, and unimpaired patients. Therefore, the PVT might be particularly well suited for the diagnosis and quantification of the mildest forms of overt HE, which are characterised by somnolence and/or lethargy, together with neurophysiological features reminiscent of the transition from wake-to-sleep (*i.e.* anteriorisation of the EEG background rhythm[47] and mild EEG slowing[36]). This hypothesis is also supported by the predictive value of PVT parameters in relation to the subsequent development of HE-related hospitalisations, and death. Of note, in the current study, we only used a limited set of direct PVT parameters. There are several derived, validated PVT parameters that might also be of interest in this patient population, such as the so-called RRT-slope (*i.e.* the linear regression of the slope of the reciprocal of the reaction time, expressed in seconds).[21,48]

The effect of disease on driving ability is an issue of primary importance, because motor vehicle accidents are associated with considerable morbidity and mortality, as well as direct and indirect economic and societal costs.[49] For example, a large body of research indicates that cognitive impairment severely impinges on driving abilities in older patients.[50–53] There is also evidence that, on average, patients with minimal and/or overt HE are worse drivers than healthy volunteers of comparable age, based on neuropsychological testing of cognitive domains that are thought to be implicated in driving,[54] simulated driving on virtual navigators,[23] or actual on-the-road performance.[3,4] However, it remains difficult to predict driving ability at an individual patient level,[4] because driving is a complex competence that depends on a variety of factors, including natural inclination, experience and practice. Indeed, in one of the first studies on driving and HE, Srivastava and colleagues described the case of a taxi driver with cirrhosis and significant neuropsychological impairment whose on-the-road performance remained excellent.[55] Both relaxed and strict approaches to HE and driving might lead to problems: on the one hand, one would not want dangerous drivers within the community but, on the other hand, it would be unfair to impinge on patients' earning ability and their social lives by depriving them of their licence unnecessarily. A diagnosis of minimal or covert HE does not imply that the patient is a dangerous driver.

In addition, although it has been assumed that neuropsychological measures of minimal or covert HE (and pertinent abnormality thresholds) might be of use in assessing driving ability, there is no proof that this is indeed the case. In Italy, cirrhosis is not listed among the diseases for which medical check-ups and reports are compulsory for the obtainment or renewal of a driving licence. In addition, doctors are not trained to evaluate fitness to drive and neither are they legal representatives. Therefore, they act in the best interests of both the patients and society by following applicable local laws. On the other hand, doctors cannot avoid the responsibility of counselling patients with diagnosed HE on the possible dangers of their driving and, often, the safest advice is to stop driving until the responsible authorities have formally cleared the patient. In difficult situations, the doctor can resort to direct consultation with the bodies that have the expertise to test driving ability and the authority to grant, renew or revoke the licence. It would appear reasonable to apply driving restrictions to patients with any degree of overt HE, but even in this respect neither available data nor regulations are compelling. We ourselves often receive referrals including specific questions on driving from general practitioners, colleagues in district hospitals and even the driving authorities, to which we tend to respond with a comprehensive clinical and neuropsychiatric evaluation for subsequent legal steps and decisions on the licence. On a less formal basis, families and caregivers also often ask for advice. By contrast, patients with HE are generally optimistic about their driving abilities. In a study by Kircheis *et al.*, 96% of patients with minimal HE were convinced that they were good or very good drivers, compared with 92% of control subjects.[4] This is likely to relate to a certain degree of frontalisation and lack of insight into their condition, which characterises patients with mild forms of HE. Sherlock and Dooley famously described them as 'co-operative, pleasant individuals, with an ease in social relationships and a playful, euphoric mood'.[56] Indeed, in our own study, both patients who drove without a licence had some degree of overt HE, possibly leading to an underestimation of both difficulties and risks. In addition, a further 7 patients with some degree of overt HE also drove, but with a licence. It is possible that these individuals had an appreciation of their driving difficulties but needed to use the car for stringent work or personal reasons. However, this hypothesis is not supported by the data on distance driven, which was extremely limited in all instances, suggesting that nobody really drove regularly for work and/or personal reasons. When analysing these data, one should also consider that Italian society is still characterised by strong family bonds (most patients come to medical appointments with family), and the country is small and well served by public transport. These aspects, and thus the availability of alternatives (other driver within the family or public transport) might influence the choice and/or adherence to medical advice in relation to driving. This might also in some way justify both doctors and family members who, in our experience, are fairly proactive in restricting individuals who appear at risk. In our series, common sense and clinical sense seemed to work reasonably well in this respect, as patients who did not drive despite having a licence had worse PVT, PHES and EEG performances compared to those who had a licence and drove. In addition, when patients who had stopped driving because of HE-related reasons were modelled as having had an accident and/or fine over the subsequent 6 and 12 months, the PVT-derived parameter lapses were a predictor of outcome, even after correction for MELD and age. Similar results were obtained with the ICT, which appeared to be associated with a significantly higher crash rate on a prospective follow-up period in patients with minimal and/or covert HE compared with unimpaired subjects.[57]

The PVT is an interesting tool in this setting, because somnolence and reduced vigilance are generally perceived as dangerous in relation to driving,[58–65] might be HE features that alarm caregivers and doctors, and are well measured by PVT-derived parameters. The fact that neither novel nor standard HE indices predicted traffic violations or road traffic accidents is likely related to the fact that the potentially dangerous drivers within the series did not drive despite having a licence, probably as a result of recommendations from family and/or doctors.

In conclusion, the PVT is a test of vigilance, which is fairly stable in the healthy population, performs well as an HE index, especially in mild forms of overt HE, and might have a role in identifying dangerous drivers among patients with cirrhosis. Further studies seem warranted to validate these findings and to identify relevant PVT abnormality thresholds for use in patients with cirrhosis for both purposes of HE quantification and the assessment of fitness to drive.

Financial support

The work was partly funded by a grant from the Italian Ministry of Health to S.M. (Giovani Ricercatori 2009–1604309).

Conflict of interest

The authors declare that they have no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contribution

C.F.: Patient recruitment and study, data analysis, manuscript drafting. M.D.R.: patient recruitment and study, data analysis, manuscript drafting. M.Z.: patient recruitment and study. S.C.: patient recruitment and study. L.Z.: patient recruitment and study. M.S.: patient recruitment, manuscript revision for important intellectual content. P.B.: study design, patient recruitment, manuscript revision for important intellectual content. P.An.: manuscript revision for important intellectual content. P.Am.: data analysis, manuscript revision for important intellectual content. S.M.: study design, funding, patient recruitment, data analysis, manuscript drafting.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.12.031.

References

[1] Watanabe A, Tuchida T, Yata Y, Kuwabara Y. Evaluation of neuropsychological function in patients with liver cirrhosis with special reference to their driving ability. Metab Brain Dis 1995;10:239–248.
[2] Bajaj JS, Pinkerton SD, Sanyal AJ, Heuman DM. Diagnosis and treatment of minimal hepatic encephalopathy to prevent motor vehicle accidents: a cost-effectiveness analysis. Hepatology 2012;55:1164–1171.
[3] Wein C, Koch H, Popp B, Oehler G, Schauder P. Minimal hepatic encephalopathy impairs fitness to drive. Hepatology 2004;39:739–745.

[4] Kircheis G, Knoche A, Hilger N, Manhart F, Schnitzler A, Schulze H, et al. Hepatic encephalopathy and fitness to drive. Gastroenterology 2009;137:1706–1715.
[5] Bajaj JS, Thacker LR, Heuman DM, Gibson DP, Sterling RK, Stravitz RT, et al. Driving simulation can improve insight into impaired driving skills in cirrhosis. Dig Dis Sci 2012;57:554–560.
[6] Montagnese S, Turco M, Amodio P. Hepatic encephalopathy and sleepiness: an interesting connection? J Clin Exp Hepatol 2015;5:S49–S53.
[7] Dinges DF, Powell JW. Sleepiness is more than lapsing. J Sleep Res 1988;17:84.
[8] Loh S, Lamond N, Dorrian J, Roach G, Dawson D. The validity of psychomotor vigilance tasks of less than 10-minute duration. Behav Res Methods Instruments Comput 2004;36:339–346.
[9] Thomann J, Baumann CR, Landolt H-P, Werth E. Psychomotor vigilance task demonstrates impaired vigilance in disorders with excessive daytime sleepiness. J Clin Sleep Med 2014;10:1019–1024.
[10] Fronczek R, Raymann RJEM, Romeijn N, Overeem S, Fischer M, van Dijk JG, et al. Manipulation of core body and skin temperature improves vigilance and maintenance of wakefulness in narcolepsy. Sleep 2008;31:233–240.
[11] Basner M, Dinges DF. Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. Sleep 2011;34:581–591.
[12] Matthews RW, Ferguson SA, Sargent C, Zhou X, Kosmadopoulos A, Roach GD. Using interstimulus interval to maximise sensitivity of the Psychomotor Vigilance Test to fatigue. Accid Anal Prev 2017;99:406–410.
[13] Grant DA, Honn KA, Layton ME, Riedy SM, Van Dongen HPA. 3-minute smartphone-based and tablet-based psychomotor vigilance tests for the assessment of reduced alertness due to sleep deprivation. Behav Res Methods 2017;49:1020–1029.
[14] Gander P, Mulrine HM, van den Berg MJ, Wu L, Smith A, Signal L, et al. Does the circadian clock drift when pilots fly multiple transpacific flights with 1- to 2-day layovers? Chronobiol Int 2016;33:982–994.
[15] Zhang C, Varvarigou V, Parks PD, Gautam S, Bueno AV, Malhotra A, et al. Psychomotor vigilance testing of professional drivers in the occupational health clinic: a potential objective screen for daytime sleepiness. J Occup Environ Med 2012;54:296–302.
[16] Narciso FV, Barela JA, Aguiar SA, Carvalho ANS, Tufik S, de Mello MT. Effects of shift work on the postural and psychomotor performance of night workers. PLoS ONE 2016;11 e0151609.
[17] Park M, Hood MM, Shah RC, Fogg LF, Wyatt JK. Sleepiness, parkinsonian features and sustained attention in mild Alzheimer's disease. Age Ageing 2012;41:765–770.
[18] Kim H, Dinges DF, Young T. Sleep-disordered breathing and psychomotor vigilance in a community-based sample. Sleep 2007;30:1309–1316.
[19] Mackworth JF. Vigilance, arousal, and habituation. Psychol Rev 1968;75:308–322.
[20] Powell NB, Riley RW, Schechtman KB, Blumen MB, Dinges DF, Guilleminault C. A comparative model: reaction time performance in sleep-disordered breathing versus alcohol-impaired controls. Laryngoscope 1999;109:1648–1654.
[21] Dinges DF, Pack F, Williams K, Gillen KA, Powell JW, Ott GE, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. Sleep 1997;20:267–277.
[22] Basner M, Mollicone D, Dinges DF. Validity and sensitivity of a Brief Psychomotor Vigilance Test (PVT-B) to total and partial sleep deprivation. Acta Astronaut 2011;69:949–959.
[23] Bajaj JS, Saeian K, Verber MD, Hischke D, Hoffmann RG, Franco J, et al. Inhibitory Control Test is a simple method to diagnose minimal hepatic encephalopathy and predict development of overt hepatic encephalopathy. Am J Gastroenterol 2007;102:754–760.
[24] Amodio P, Schiff S, Del Piccolo F, Mapelli D, Gatta A, Umiltà C. Attention dysfunction in cirrhotic patients: an inquiry on the role of executive control, attention orienting and focusing. Metab Brain Dis 2005;20:115–127.
[25] Bajaj JS, Thacker LR, Heuman DM, Fuchs M, Sterling RK, Sanyal AJ, et al. The Stroop smartphone application is a short and valid method to screen for minimal hepatic encephalopathy. Hepatology 2013;58:1122–1132.
[26] Amodio P, Del Piccolo F, Marchetti P, Angeli P, Iemmolo R, Caregaro L, et al. Clinical features and survivial of cirrhotic patients with subclinical cognitive alterations detected by the number connection test and computerized psychometric tests. Hepatology 1999;29:1662–1667.
[27] Montagnese S, Schiff S, Turco M, Bonato CA, Ridola L, Gatta A, et al. Simple tools for complex syndromes: a three-level difficulty test for hepatic encephalopathy. Dig Liver Dis 2012;44:957–960.
[28] Lauridsen MM, Grønbæk H, Næser EB, Leth ST, Vilstrup H. Gender and age effects on the continuous reaction times method in volunteers and patients with cirrhosis. Metab Brain Dis 2012;27:559–565.
[29] Lauridsen MM, Thiele M, Kimer N, Vilstrup H. The continuous reaction times method for diagnosing, grading, and monitoring minimal/covert hepatic encephalopathy. Metab Brain Dis 2013;28:231–234.
[30] Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–649.
[31] Kamath P, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.
[32] Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology 1977;72:573–583.
[33] Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60:715–735.
[34] Weissenborn K, Ennen JC, Schomerus H, Rückert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. J Hepatol 2001;34:768–773.
[35] Amodio P, Campagna F, Olianas S, Iannizzi P, Mapelli D, Penzo M, et al. Detection of minimal hepatic encephalopathy: normalization and optimization of the Psychometric Hepatic Encephalopathy Score. A neuropsychological and quantified EEG study. J Hepatol 2008;49:346–353.
[36] Van der Rijt CC, Schalm SW, De Groot GH, De Vlieger M. Objective measurement of hepatic encephalopathy by means of automated EEG analysis. Electroencephalogr Clin Neurophysiol 1984;57:423–426.
[37] Amodio P, Marchetti P, Del Piccolo F, de Tourtchaninoff M, Varghese P, Zuliani C, et al. Spectral versus visual EEG analysis in mild hepatic encephalopathy. Clin Neurophysiol 1999;110:1334–1344.
[38] Jones CB, Dorrian J, Jay SM, Lamond N, Ferguson S, Dawson D. Self-awareness of impairment and the decision to drive after an extended period of wakefulness. Chronobiol Int 2006;23:1253–1263.
[39] Correa A, Molina E, Sanabria D. Effects of chronotype and time of day on the vigilance decrement during simulated driving. Accid Anal Prev 2014;67:113–118.
[40] Rodríguez-Morilla B, Madrid JA, Molina E, Pérez-Navarro J, Correa Á. Blue-enriched light enhances alertness but impairs accurate performance in evening chronotypes driving in the morning. Front Psychol 2018;9:688.
[41] Anund A, Fors C, Ihlström J, Kecklund G. An on-road study of sleepiness in split shifts among city bus drivers. Accid Anal Prev 2018;114:71–76.
[42] McManus B, Heaton K, Stavrinos D. Commercial motor vehicle driving performance: an examination of attentional resources and control using a driving simulator. J Exp Psychol Appl 2017;23:191–203.
[43] Kosmadopoulos A, Sargent C, Zhou X, Darwent D, Matthews RW, Dawson D, et al. The efficacy of objective and subjective predictors of driving performance during sleep restriction and circadian misalignment. Accid Anal Prev 2017;99:445–451.
[44] Schwarz JFA, Geisler P, Hajak G, Zulley J, Rupprecht R, Wetter TC, et al. The effect of partial sleep deprivation on computer-based measures of fitness to drive. Sleep Breath 2016;20:285–292.
[45] Perrier J, Bertran F, Marie S, Couque C, Bulla J, Denise P, et al. Impaired driving performance associated with effect of time duration in patients with primary insomnia. Sleep 2014;37:1565–1573.
[46] Jackson ML, Croft RJ, Kennedy GA, Owens K, Howard ME. Cognitive components of simulated driving performance: sleep loss effects and predictors. Accid Anal Prev 2013;50:438–444.
[47] Montagnese S, Jackson C, Morgan MY. Spatio-temporal decomposition of the electroencephalogram in patients with cirrhosis. J Hepatol 2007;46:447–458.
[48] Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. Behav Res Methods, Instruments, Comput 1985;17:652–655.
[49] UNECE. Statistics of Road Traffic Accidents in Europe and North America. Geneva: UNECE; 2011.
[50] Beratis IN, Pavlou D, Papadimitriou E, Andronas N, Kontaxopoulou D, Fragkiadaki S, et al. Mild Cognitive Impairment and driving: does in-vehicle distraction affect driving performance? Accid Anal Prev 2017;103:148–155.

[51] Devlin A, McGillivray J, Charlton J, Lowndes G, Etienne V. Investigating driving behaviour of older drivers with mild cognitive impairment using a portable driving simulator. Accid Anal Prev 2012;49:300–307.
[52] Park S-W, Choi ES, Lim MH, Kim EJ, Hwang S Il, Choi K-I, et al. Association between unsafe driving performance and cognitive-perceptual dysfunction in older drivers. PM R 2011;3:198–203.
[53] Freund B, Colgrove LA, Petrakos D, McLeod R. In my car the brake is on the right: pedal errors among older drivers. Accid Anal Prev 2008;40:403–409.
[54] Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Dölle W. Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. Dig Dis Sci 1981;26:622–630.
[55] Srivastava A, Mehta R, Rothke SP, Rademaker AW, Blei AT. Fitness to drive in patients with cirrhosis and portal-systemic shunting: a pilot study evaluating driving performance. J Hepatol 1994;21:1023–1118.
[56] Sherlock S, Dooley J. Diseases of the Liver and Biliary System. 11th ed. Oxford: Blackwell Publishing; 2002.
[57] Bajaj JS, Saeian K, Schubert CM, Hafeezullah M, Franco J, Varma RR, et al. Minimal hepatic encephalopathy is associated with motor vehicle crashes: the reality beyond the driving test. Hepatology 2009;50:1175–1183.
[58] Lee ML, Howard ME, Horrey WJ, Liang Y, Anderson C, Shreeve MS, et al. High risk of near-crash driving events following night-shift work. Proc Natl Acad Sci U S A 2016;113:176–181.
[59] Dawson D, Reynolds AC, Van Dongen HPA, Thomas MJW. Determining the likelihood that fatigue was present in a road accident: a theoretical review and suggested accident taxonomy. Sleep Med Rev 2018;42:202–210.
[60] Al-Libawy H, Al-Ataby A, Al-Nuaimy W, Al-Taee MA. Modular design of fatigue detection in naturalistic driving environments. Accid Anal Prev 2018;120:188–194.
[61] Cardoso M, Fulton F, Callaghan JP, Johnson M, Albert WJ. A pre/post evaluation of fatigue, stress and vigilance amongst commercially licensed truck drivers performing a prolonged driving task. Int J Occup Saf Ergon 2018:1–11.
[62] Mollicone D, Kan K, Mott C, Bartels R, Bruneau S, van Wollen M, et al. Predicting performance and safety based on driver fatigue. Accid Anal Prev 2018. https://doi.org/10.1016/j.aap.2018.03.004.
[63] Williamson A, Lombardi DA, Folkard S, Stutts J, Courtney TK, Connor JL. The link between fatigue and safety. Accid Anal Prev 2011;43:498–515.
[64] Wang S-Y, Wu K-F. Reducing intercity bus crashes through driver rescheduling. Accid Anal Prev 2018;122:25–35.
[65] Williamson AM, Feyer AM, Friswell R. The impact of work practices on fatigue in long distance truck drivers. Accid Anal Prev 1996;28:709–719.