Attention following traumatic brain injury: Neuropsychological and driving simulator data, and association with sleep, sleepiness, and fatigue

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Abstract

The objectives of this study were to compare individuals with TBI and healthy controls on neuropsychological tests of attention, driving simulation performance, and explore their relationships with participants' characteristics, sleep, sleepiness, and fatigue. Participants were 22 adults with moderate or severe TBI (time since injury ≥ one year) and 22 matched controls. They completed three neuropsychological tests of attention, a driving simulator task, nighttime polysomnographic recordings, and subjective ratings of sleepiness and fatigue. Results showed that participants with TBI exhibited poorer performance compared to controls on measures tapping speed of information processing and sustained attention, but not on selective attention measures. On the driving simulator task, a greater variability of the vehicle lateral position was observed in the TBI group. Poorer performance on specific subsets of neuropsychological variables was associated with poorer sleep continuity in the TBI group, and with a greater increase in subjective sleepiness in both groups. No significant relationship was found between cognitive performance and fatigue. These findings add to the existing evidence that speed of information processing is still impaired several years after moderate to severe TBI. Sustained attention could also be compromised. Attention seems to be associated with sleep continuity and daytime sleepiness; this interaction needs to be explored further.

Keywords: traumatic brain injury, cognition, sleep disturbances, neuropsychological tests, driving simulator

Introduction

Traumatic brain injury (TBI) is a leading cause of death and long-term disability worldwide. An estimated 1.7 million people sustain a TBI every year in the United States, 16.3% (94 per 100 000) of those injuries necessitating an hospitalization (Faul, Xu, Wald, & Coronado, 2010). Though far less prevalent than mild TBI, moderate and severe injuries represent a critical public health issue due to high individual, familial, and societal costs associated with extensive rehabilitation needs and chronic disability (Lezak, Howieson, Bigler, & Tranel, 2012). Persistent cognitive impairment is a hallmark feature of moderate to severe TBI, both in the early stages of recovery and in the long run (Ruttan, Martin, Liu, Colella, & Green, 2008).

While there is extensive heterogeneity in the neuropathological presentation of TBI, cognitive deficits are thought to result mainly from diffuse axonal injury and focal lesions concentrated in the anterior brain regions (McCullagh & Feinstein, 2011). Thus, it is not surprising that impairments in attention are among the most pervasive cognitive problems (Azouvi, Vallat-Azouvi, & Belmont, 2009). Current evidence on attentional functioning following moderate to severe TBI highlights a reduction in speed of information processing, which is persisting several years after the injury. However, regarding the presence of specific deficits in selective, divided, and sustained attention, there is a lack of consensus (Mathias & Wheaton, 2007; McCullagh & Feinstein, 2011). Some authors suggested that the general slowness of speed of information processing is sufficient to explain deficits found in tasks presumably assessing other types of attention (Ponsford & Kinsella, 1992; Spikman, van Zomeren, & Deelman, 1996). Others studies revealed impairments in divided attention, supervisory control, and sustained attention, but solely in complex tasks associated with a high cognitive load and emphasizing control over speed (Azouvi et al., 2009; Park, Moscovitch, & Robertson, 1999).

Attention problems have been shown to compromise the resolution or adaptation to crucial challenges of life after TBI such as return to work (Crépeau & Sherzer, 1993) and driving (Brouwer, Withaar, Tant, & van Zomeren, 2002). While most studies have used clinically-based

neuropsychological tests or theoretically-based computerized tasks to measure cognitive functioning, some researchers have advocated for the use of more ecologically valid tools. Among these, driving simulators are of particular interest in the TBI population. Whereas about 50% of individuals with moderate to severe TBI resume driving, residual cognitive deficits typically represent the main barrier for those who fail to do so (Brouwer et al., 2002; Novack et al., 2010). In fact, driving solicits a wide range of cognitive functions typically affected by TBI, especially in the attentional domain (e.g., information processing speed, divided attention) (Brouwer et al., 2002). For instance, a recent study showed that participants with TBI who had returned to driving performed significantly better on the Trail Making Test, a widely used attention test, compared to participants who had not returned to driving (Cullen, Krakowski, & Taggart, 2014). In addition to clinical neuropsychological tests, driving simulators, presumably presenting higher ecological validity, have been used as a proxy for cognitive performance. Some studies observed poorer performance in TBI compared with control individuals on variables such as crash rate, reaction time or accuracy on concomitant tasks, or variability of vehicle position on the roadway (Chaumet et al., 2008; Cyr et al., 2009; Lengenfelder, Schultheis, Al-Shihabi, Mourant, & DeLuca, 2002). The latter variable, a measure of vehicle control, is one of the most commonly used outcome measures in driving simulator studies. Greater variability of the lateral position can be conceptualized as riskier driving, as it may be associated with poorer adjustment to changes in road parameters (e.g., curvature), increased probability of a centreline crossing or a road-edge excursion, and, ultimately, greater risk of accident (Verster & Roth, 2011). It has also been shown to be affected by fatigue (Du, Zhao, Zhang, Zhang, & Rong, 2015).

Several factors have been postulated to adversely impact already-compromised cognitive functioning following TBI (McCullagh & Feinstein, 2011). Sleep-wake disturbances and fatigue are prime examples of such factors. Indeed, 50% of individuals with TBI suffer from sleep disturbances and 25-29% meet diagnostic criteria for a sleep disorder (Mathias & Alvaro, 2012),

while 43-73% report chronic fatigue (Belmont, Agar, Hugeron, Gallais, & Azouvi, 2006). Only a handful of studies have documented the association between cognition and sleep-wake functions in the TBI population. A study comparing self-defined good and poor sleepers revealed that the latter displayed worse sustained attention (Bloomfield, Espie, & Evans, 2010). Similar findings were reported for daytime sleepiness, with poorer attentional performance in sleepy compared to non-sleepy individuals with TBI (Castriotta et al., 2007), and in patients with TBI and obstructive sleep apnoea (OSA) compared to patients without OSA (Wilde et al., 2007). Studies examining the interaction between attention and fatigue have shown that performing a challenging sustained attention task was associated with greater psychological (e.g. subjective report of fatigue or mental effort) or physiological (e.g. increase in blood pressure or changes in brain activity) costs in individuals with TBI compared to healthy controls (Azouvi et al., 2004; Belmont, Agar, & Azouvi, 2009; Kohl, Wylie, Genova, Hillary, & Deluca, 2009; Riese, Hoedemaeker, Brouwer, & Mulder, 1999; Ziino & Ponsford, 2006a, 2006b). According to the coping hypothesis, these fatigue-related costs are the manifestations of the compensatory effort required by individuals with TBI in order to maintain a desired level of performance (van Zomeren, Brouwer, & Deelman, 1984).

To sum up, impairments in attentional functions, particularly in speed of information processing, are an almost universal persistent consequence of moderate to severe TBI. These deficits are seen on clinical neuropsychological tests, as well as on more ecologically valid instruments. These deficits can potentially interact with sleep-wake disturbances and fatigue, also very prevalent sequelae of TBI. To date, no study has investigated the relationships between well-validated and commonly used clinical neuropsychological tests, driving simulation performance as a functional outcome with higher ecological validity, and measures of objective sleep (polysomnography), and subjective sleepiness and fatigue. The first objective of the present study was to compare participants with TBI and healthy controls on three clinical neuropsychological measures of attention. The second objective was to compare the TBI and

control groups on driving simulation performance, namely the occurrence of events (e.g., accidents, centreline crossings) and time-dependent measures (e.g., variability of the lateral position of the vehicle). It was hypothesized that the TBI group would perform significantly more poorly on neuropsychological measures tapping speed of processing and sustained attention, and would show greater variability of lateral position on the driving simulator, suggesting poorer vehicle control. The third objective was to explore within each group the relationships between performance on neuropsychological tests and the driving simulator task, and measures of sleep, sleepiness, and fatigue. A significant association was expected between poorer attention performance and poorer sleep continuity the night before testing and a greater increase in sleepiness and fatigue following testing.

Methods

The study protocol was approved by the Institutional Research Ethics Boards of the *Institut de réadaptation en déficience physique de Québec* and the *Centre de recherche de l'Institut universitaire en santé mentale de Québec*, both affiliated with Université Laval, Québec, Québec, Canada. Study participants and procedure have been described in more details in a paper reporting group comparisons on sleepiness, fatigue, and sleep measures (Beaulieu-Bonneau & Morin, 2012).

Participants and procedure

Participants with TBI (N = 22) had to be aged between 18 and 59 years old and have sustained a moderate or severe TBI at least one year prior to their participation in the study. They were recruited through a review of medical records (n = 8) and referrals from healthcare professionals (n = 6) of a local rehabilitation centre, and from solicitation of members of a regional association of TBI survivors (n = 8). TBI severity was extracted from the medical records and was based on an algorithm taking into account the presence and duration of loss of consciousness, duration of post-traumatic amnesia (PTA), initial score on the Glasgow Coma Scale (Teasdale & Jennett, 1974), results of brain imaging, and findings from neurological exam

(Ministère de la santé et des services sociaux du Québec & Société d'assurance automobile du Québec, 2005). Healthy controls (*N* = 22) were matched with participants with TBI on gender, age (± 3 years), and education (± 3 years or same highest academic degree). They were recruited through personal referrals (*n* = 8), referrals from on-going studies at the sleep centre (*n* = 3), and advertisements in educational and healthcare institutions (*n* = 11). To ensure prior driving experience, participants had to either hold a driver's license or have held one in the past. Exclusion criteria for all participants were: (a) active or progressive medical condition susceptible to interfere with sleep-wake or cognitive functions (e.g. epilepsy, cancer); (b) sensory or motor impairment potentially affecting test administration or performance; (c) history of bipolar or psychotic disorder; (d) current major depressive episode; (e) evidence of a sleep-related breathing disorder; (f) regular use of hypnotic or antidepressant medication (unless dosage had been stable for at least three months); (g) night- or rotating-shift work within the past year; and (h) atypical sleep-wake schedule (i.e. habitual bedtime later than 2:00 a.m. or habitual rising time later than 10:00 a.m.).

The study involved two visits to the sleep centre. The first visit consisted in obtaining informed consent, verifying selection criteria, filling out self-reported measures, and completing the practice scenario on the driving simulator. Figure 1 presents the complete procedure of the second visit. The second visit involved one night of polysomnographic recording and, on the following day, completion of three neuropsychological tests (morning, about 2-3 hours after arising time), a driving simulator task (afternoon, about 5-6 hours after arising time), and visual analogue scales (every hour, starting from arising time). Participants also underwent four trials of the Maintenance of Wakefulness Test, a daytime polysomographic measure of sleepiness during which the participant is asked to remain awake as long as possible (until discontinuation of the trial after 40 min if no sleep occurred) while sitting on a bed in a dark and quiet room. These trials took place right before (first) and about 30 min after (second) the neuropsychological tests, and right before (third) and about 30 min after (fourth) the driving

simulator task. Results from this test are available elsewhere (Beaulieu-Bonneau & Morin, 2012). During the experimental day, participants were asked to use their medication as usual and limit their caffeine intake to one cup at breakfast to avoid inter-individual differences.

Insert Figure 1 here

Measures

Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (TMT). The D-KEFS TMT (Delis, Kaplan, & Kramer, 2001) is a variation of the original TMT consisting of five conditions: Visual Scanning (TMT-1), Number Sequencing (TMT-2; similar to original TMT, part A), Letter Sequencing (TMT-3), Number-Letter Switching (TMT-4; similar to original TMT, part B), and Motor Speed (TMT-5). Participants are asked to complete each condition as quickly as possible without making errors. The TMT is very sensitive to TBI even several years after the injury (Lezak et al., 2012). Dependent variables included completion time raw scores and age-corrected scaled scores (higher scores suggesting better performance) for each condition; and contrast raw and scaled scores comparing TMT-4 to each of the four other conditions (contrast raw scores: [TMT-4 raw score – TMT-*X* raw score] / TMT-*X* raw score; *X* = 1, 2, 3, or 5).

Auditory Consonant Trigrams (ACT). The ACT is also known as the Brown-Peterson paradigm or test of memory of three consonants (Brown, 1958; Peterson & Peterson, 1959). In each of the 15 trials of the version used in the protocol (Strauss, Sherman, & Spreen, 2006), the examiner reads three consonants followed by a number. Starting from this number, the examinee has to count out loud backwards by threes until signalled to stop (after either 9, 18, or 36 s) and asked to recall the consonants in any order. The purpose of the counting task is to prevent participants from rehearsing the consonants. Impaired performance on the ACT has been reported in a variety of neurological conditions including TBI (Strauss et al., 2006). Dependent variables were the raw scores and age-corrected z-scores (Stuss, Stethem, &

Pelchat, 1988) of the number of correctly recalled letters for the 9-, 18-, and 36-s intervals, higher scores suggesting better performance.

Continuous Performance Test II (CPT-II). Conners' CPT-II (Conners & MHS Staff, 2004) is a 14-min computerized test. Participants are asked to press the spacebar when any letter except the target letter X appears on the screen. Trials are divided into six blocks, each including 54 non-target and 6 target letters. The CPT-II differentiates clinical from non-clinical cases (Strauss et al., 2006). Dependent variables included raw scores and age- and gender-corrected T-scores (lower scores suggesting better performance) for omissions, commissions, hit reaction time (RT), variability of RT (standard error [SE]), and a measure of performance over time: RT block change (i.e. slope of change in RT over time).

Driving simulator. In addition to the three neuropsychological tests, a driving simulator was used in the study as a measure of the functional impact of attentional performance on daily activities. Driving is a complex task requiring a wide range of interacting functions, including sensory visuospatial functions, motor capacities, executive control, and several aspects of attention, including information processing speed, selective attention, divided attention, and sustained attention (Brouwer et al., 2002; Galski, Ehle, McDonald, & Mackevich, 2000). Since it mimics the real-life task of driving, simulator performance is presumably more ecologically valid than most paper-and-pencil or computer tasks. The driving simulator consisted of the STISIM Drive™ software (Systems Technology, Inc., Hawthorne, CA), a fixed-base driving cab, and three contiguous screens resulting in a 135-degree field of view. Inputs from the steering wheel, throttle, brake, turn signal switch, and horn were converted into digital signals to ensure a fluid interaction with roadway images. A 5-min practice scenario was first completed to allow participants to become familiar with the simulator environment and ascertain the presence of simulator sickness. The main scenario lasted 30 min. Participants had to drive on a low-traffic two-lane highway for 5000 m, and then on a secondary road with one lane in each direction for the remainder of the task. As the scenario was designed to explore the interaction with

sleepiness, there were no vehicles in the same direction as the driver and no passing was required. Participants were told to stay in the right-side lane and maintain their speed between 60 and 100 km/h. Data were recorded every 0.1 s starting from the 5000th meter. The scenario also included a concomitant visual attention task that required responding to different stimuli (i.e., left-, right-pointing arrow, or speakerphone symbol) appearing on the front screen by using the appropriate vehicle command (i.e., left-, right-turn switch, or horn). There were five six-symbol blocks occurring every 8000 m and consisting of two presentations of each symbol in random order. Dependent variables from the driving simulator task were the number of minor infractions committed during the driving task (including speed limit violations, centerline crossings, and road edge excursions), variability of lateral position (i.e. standard deviation [SD] of the vehicle lateral lane position with respect to the roadway dividing line), mean speed, speed variability (SD), and two measures derived from the visual attention task (i.e., mean hit reaction time, combined commission and omission error rate). The variability of lateral position, which is often used as a proxy of driving safety, is among the most commonly used dependent variables in driving simulator studies.

Polysomnography (PSG). Participants underwent one night of PSG recording. Time in bed was kept between 8 and 9 h to provide a uniform recording time across individuals. Participants' preferred sleep schedule along with logistical considerations were taken into account to determine bedtime and rising time. A standard PSG montage was used and sleep stages were scored according to standard criteria (Rechtschaffen & Kales, 1968) by experienced technologists blind to group status (i.e., TBI or control). Dependent variables were total wake time and total sleep time.

Visual analogue scales (VAS). Two 100-mm VAS, for sleepiness (VAS-s) and fatigue (VAS-f), were completed hourly on the experimental day. Instructions were given on how to differentiate sleepiness (i.e., drowsiness, sleep propensity, decreased alertness) and fatigue (i.e., weariness, weakness, depleted energy) (Pigeon, Sateia, & Ferguson, 2003). Dependent

variables were the change scores in VAS-s and -f from the ratings preceding the neuropsychological tests to the ratings following them, and the change scores from the ratings preceding the driving simulator task to the ratings following it.

Statistical analyses

All analyses were performed using IBM SPSS Statistics for Windows version 18 (IBM, 2010). Alpha level was set at two-tailed 5%. To investigate the first objective, groups were compared on raw scores from the neuropsychological measures using three MANOVAs (for dependent variables of the TMT, ACT, CPT, respectively). Univariate normality was acceptable for all variables, and no significant multivariate outlier was found for any of the three MANOVAs. Homogeneity of variance/covariance matrices across groups was respected for the MANOVAs on the ACT and CPT-II, but not for the one on the TMT. However, Tabachnik and Fidell suggest to disregard the Box M test, notoriously too sensitive, when sample size is equal across conditions (which is the case in the current study) (Tabachnik & Fidell, 2012). For each dependent variable included in the MANOVAs, effect sizes (*d*) were computed and interpreted using Cohen's criteria (Cohen, 1992). If a MANOVA reached significance, one-way ANOVAs were examined. To obtain a clinically meaningful indicator of performance, participants were classified for each dependent variable of the three neuropsychological tests as exhibiting either normal or impaired performance. The latter was defined as a standard score at least one SD (mild impairment) or two SD (moderate impairment) worse than the normative mean. Groups were then compared on the mean number of dependent variables per participant with a mild impairment or a moderate impairment using generalized linear models (Poisson distribution with log link function).

For the second objective, a MANOVA was computed to compare groups on three driving simulator variables (i.e., number of minor infractions, and mean hit reaction time, and combined commission and omission error rate from the concomitant visual attention task). The Box M test was significant, although as mentioned previously it is considered to be too sensitive when

groups are of equal sizes. The procedure described previously was applied for the MANOVA for the driving simulator task. The other variables of the driving simulator task, variability of lateral position, mean speed, and speed variability, were analysed with mixed models' repeated measures analyses of variance using a Group x Time factorial design. Best-fitting covariance matrix was set to heterogeneous compound symmetry based on Akaike's Information Criterion and Schwarz's Bayesian Criterion. The values for denominator's degrees of freedom were obtained by a Satterthwaite approximation (SPSS Inc., 2005). The Time factor consisted of five blocks of 9000 m each. As participants drove at different speeds, the distance travelled differed across participants, especially in the last block. In order to account for these inter-individual differences, data were weighted by distance travelled within each block. Group and Group × Time effects were examined, but not Time effects which would be difficult to interpret due to high inter-block heterogeneity in roadway parameters.

With regard to the analyses related to the third objective of the study, correlations were computed within each group between neuropsychological/driving simulator variables and variables derived from PSG and VAS. Non-parametric Spearman correlations were preferred because of the small sample size and robustness to non-normal distributions. To limit the number of statistical tests, correlations were computed only for neuropsychological and driving simulator variables discriminating between TBI and control participants (i.e., with significant univariate F test or significant group effect on repeated mixed models). Additionally, variables within the same test that met the latter criterion were averaged into composite scores (see Results section). Standard scores were used to compute composite scores within each neuropsychological test in order to control for age and ensure that variables were on the same scale.

Results

Sample description

Sociodemographic and clinical characteristics of study participants are presented in table 1. There were no significant between-group differences on age, education, or gender, suggesting that the matching procedure was completed as expected. Participants with TBI were significantly less likely than controls to be currently working or studying, more likely to be on long-term medical disability (i.e., receiving financial compensation for long-term medical disability from a public insurance corporation), less likely to hold a currently valid driver's license, and more likely to be using psychotropic medication. All participants with TBI had completed inpatient rehabilitation at least six months prior to their participation. Eleven participants with TBI used a total of 13 medications (11 on a daily basis): antidepressants (amitriptyline, *n* = 1; citalopram, *n* = 2; duloxetine, *n* = 1; venlafaxine, *n* = 2), hypnotics (clonazepam, *n* = 1; lorazepam, *n* = 1; zopiclone, *n* = 2), antipsychotic (quetiapine, *n* = 2), and anticonvulsive (phenitoine, *n* = 1). Control participants used a total of 4 prescribed medications (1 on a daily basis): antidepressant (venlafaxine, *n* = 1), hypnotic (zopiclone, *n* = 2), and analgesic (methylmorphine, *n* = 1). Length of driving experience did not differ significantly between groups. Because of the potential impact of medication therapeutic or side effects on the measures used in the study, we ran a series of exploratory analyses (non-parametric Mann-Whitney tests) for the TBI group only to compare medication users (*n* = 11) and non-users (*n* = 11) on all dependent variables (i.e., from neuropsychological tests, the driving simulator task, polysomnography, and visual analogue scales). There were no statistically significant differences between medication users and non-users for any of the dependent variables (*p*s ≥ 0.06). Regarding TBI characteristics, the majority of injuries were in the severe range (77.3%) and caused by a motor vehicle – traffic accident (81.8%). Time elapsed since injury varied between 13 and 141 months (mean, 53.00 SD 37.08 months). With regard to injury types reported in the medical records, 19 of 22 participants with TBI had focal contusions, 9 had

subdural hematoma, 7 had subarachnoid hemorrhage, 4 had intracerebral hemorrhage, 4 had elevated intracranial pressure, 3 had diffuse axonal injury, 3 had epidural hematoma, and 1 had subgaleal hematoma.

Insert table 1 here

First objective: Neuropsychological tests

Table 2 presents between-group comparisons on neuropsychological measures, with results of univariate analyses and effect sizes. Results of the MANOVA revealed significant differences between groups for dependent variables from the TMT, F (3, 40) = 2.38, p = 0.03, Wilks' λ = 0.61. Univariate tests showed that participants with TBI displayed significantly longer completion times compared to controls on all TMT conditions, except one (TMT-3) for which the difference was nearly-significant (p = 0.08). Groups did not significantly differ on any of the contrast scores comparing the switching condition (TMT-4) to each of the four other conditions.

For the ACT, the MANOVA showed significant differences between the TBI and control groups, F (3, 40) = 3.26, p = 0.03; Wilks' λ = 0.80. One-way ANOVAs revealed that individuals with TBI correctly recalled a significantly lower number of letters compared to controls for the 9-s interval of the ACT, but groups did not differ for the 18- or 36-s intervals. The MANOVA for CPT-II variables also reached statistical significance, F (3, 40) = 3.77, p < 0.01, Wilks' λ = 0,67. Univariate tests showed that compared to their control counterparts, participants with TBI displayed significantly slower mean reaction time and greater variability in reaction time. On the measure of performance over time, groups significantly differed: the TBI group presented a positive mean slope, suggesting slowing in reaction time as the test progressed, while the control group exhibited a negative mean slope, indicating increasing quickness as the test progressed. There were no significant between-group differences on the number of omissions or commissions. Of note, all significant univariate comparisons for the TMT, ACT, and CPT-II yielded moderate to large effect sizes ($0.64 \leq d \leq 1.02$).

Insert table 2 here

Participants with impaired performance (i.e. standard score at least one SD [mild impairment] or two SD [moderate impairment] worse than the normative mean) were identified for the 17 neuropsychological variables. The mean number of mild impairments per participant was significantly different between groups (TBI, 3.82 SD 2.44 vs. control, 1.68 SD 1.43), Wald $X^2(1, N = 44) = 17.27$, $p < 0.01$, as was the mean number of moderate impairments, (TBI, 0.91 SD 1.23 vs. control, 0.32 SD 0.57), Wald $X^2(1, N = 44) = 5.72$, $p = 0.02$.

Second objective: Driving simulator task

None of the 44 participants reported significant symptoms of simulator sickness (e.g., nausea, dizziness) while performing the practice or the experimental driving task. Only one major infraction (collision) was recorded, in the TBI group. The MANOVA for the three driving simulator variables (minor infractions, and mean hit reaction time and error rate from the visual attention task) was not significant, suggesting that TBI and control groups were comparable, $F(3, 40) = 1.96$, $p = 0.14$, Wilks' $\lambda = 0{,}87$. Therefore, univariate tests were not computed (see Table 2 for means, standard deviations, and effect sizes for TBI and control groups). Results for the variability of lateral position per group over time are displayed on figure 2. A significant Group effect was found, $F(1, 56) = 8.53$, $p < 0.01$, with greater position variability in the TBI group (estimated marginal mean ± SE: TBI, 0.40 ± 0.02 vs. control, 0.33 ± 0.02 m). Group × Time interaction was nearly significant, $F(4, 55) = 2.36$, $p = 0.07$, with greater position variability in the latter blocks in the TBI group. Group and Group × Time interaction effects did not reach statistical significance for mean speed or speed variability (ps ≥ 0.07).

Insert figure 2 here

Third objective: Association between attention and sleep, sleepiness, and fatigue

Neuropsychological and driving simulator variables selected to explore relationships with sleep/fatigue characteristics included nine variables with a significant difference between the TBI and control groups (eight with a significant univariate test as presented in table 2, and one with a significant group effect in mixed model analyses). In order to reduce the number of statistical analyses and to facilitate results interpretation, for variables within the same test, standard scores were combined into composite scores, yielding four variables: (1) *TMT-composite,* averaging completion time scaled scores of conditions 1, 2, 4, and 5 of the TMT; (2) z-score of the number of correctly recalled letters for the 9-s interval on the ACT; (3) *CPT-composite,* averaging T-scores of reaction time, reaction time SE, and RT block change; and (4) variability of lateral position on the driving simulator. Spearman correlations were computed between these four variables, and none was significant, either in the TBI or control group (rs < 0.31, ps ≥ 0.16). This suggests that these variables measure distinct attentional aspects.

In the TBI group, poorer performance on TMT-composite score was significantly correlated with longer PSG-measured total wake time, $r_s(n = 22) = -0.60$, $p < 0.01$, and shorter total sleep time, $r_s(n = 22) = 0.45$, $p = 0.04$, on the night preceding testing; those relationships were not significant in the control group (ps ≥ 0.25). A significant correlation was found between poorer performance on the CPT-composite score and a greater increase in VAS-s from the rating preceding to the rating following neuropsychological testing, in both the TBI, $r_s(n = 21) = 0.55$, $p < 0.01$; and control group, $r_s(n = 22) = 0.52$, $p = 0.01$. The z-score of the 9-s interval on the ACT and the variability of lateral position on the driving simulator task did not correlate with any sleep, sleepiness, or fatigue measures in either group.

Discussion

This study aimed to assess attentional functioning following moderate to severe TBI using standardized neuropsychological instruments and a driving simulator task. Analyses revealed that individuals with TBI assessed 1-11 years post-injury exhibited poorer attentional

performance compared with matched healthy controls on neuropsychological measures tapping speed of information processing and sustained attention, with moderate to large effect sizes. On the driving simulator task, individuals with TBI showed a greater variability of the vehicle lateral position. Another objective of the present study was to explore the correlates of attentional functioning. Performance on specific neuropsychological measures appeared to be associated with sleep in the TBI group, and with an increase in subjective sleepiness in both groups. No significant relationships were documented between cognitive performance and subjective fatigue.

The current findings add to the evidence that reduced speed of information processing is the most consistent attentional deficit following moderate to severe TBI (Azouvi et al., 2009; Mathias & Wheaton, 2007; McCullagh & Feinstein, 2011). While this is believed to be one of the first studies reporting data on the D-KEFS TMT and Conners' CPT-II in the context of TBI, similar results (i.e. slower or more variable completion or reaction times) were obtained with the original TMT and the first version of the CPT (Dimoska-Di Marco, McDonald, Kelly, Tate, & Johnstone, 2011; Mathias & Wheaton, 2007). In the current study, there was no indication of a selective attention deficit, as indicated by the absence of group differences on TMT contrast scores or on the number of commission errors on the CPT-II. However, CPT-II findings revealed progressive slowing in reaction time over time in the TBI group relative to the control group. Whereas most previous studies have failed to observe a time-dependent performance deterioration, increasing variability over time has been found in some studies (Azouvi et al., 2009).

With regard to the ACT, previous studies using variations of the Brown-Peterson paradigm have found a load-dependent impairment, with individuals with TBI performing more poorly compared to controls on longer time intervals between the presentation and the recall of the letters (Vallat-Azouvi, Weber, Legrand, & Azouvi, 2007). Contrasting results have been observed in the present study, with a significant group difference for the shorter interval only.

Performance was fairly constant across the three time intervals in the TBI group, while it gradually dropped in the control group (which is expected according to normative values). It could be hypothesized that individuals with TBI require more time to process or consolidate the information while performing the concomitant counting task (K. A. Stokes, personal communication, February 29, 2012), thus impairing their performance after a shorter time interval but not at longer intervals. This should be investigated further.

The clinical significance of neuropsychological deficits has seldom been addressed in studies on post-TBI cognitive functioning, and thus it represents a strength of the present investigation. Whereas participants with TBI were more likely to perform at least one SD below normative values, most of these impaired performances could be classified as mild (i.e., between 1 and 2 SD below the mean), and average performances were, for the most part, within the normal range. This could suggest that the sample was highly functional relative to the whole TBI population, although more than half of the participants were on long-term medical disability. It is also possible that the tests administered in the study did not target the problematic cognitive areas for a certain proportion of participants (e.g., memory, higher-order executive functions). Indeed, important inter-individual differences exist in the nature and severity of long-term cognitive deficits, presumably related to the heterogeneity of TBI characteristics and recovery course (Lezak et al., 2012).

Regarding the driving simulator, results corroborate previous findings of an increased variability of lateral position in individuals with TBI (Chaumet et al., 2008). This is also consistent with neuropsychological findings, as this variable is believed to measure speed of information processing and fluctuation in attention. Although the variability of the vehicle lateral position is often used as a measure of driving safety, it is unclear whether the magnitude of the difference seen between the control and TBI groups on this variable in the present study truly represents a higher risk of accident in the TBI group. There are no standard criteria to determine when the variability of lateral position becomes unsafe, as it depends on the type of driving simulator,

roadway parameters, and instructions given to participants. The fact that groups were not significantly different on the occurrence of centreline crossings and road-edge excursions, which are extreme values of lateral position, points towards the absence of a marked risk of accident in the TBI group as a whole. Although there was no significant interaction for any of the three variables analysed with repeated measures, there was a non-significant trend suggesting that in later time blocks, the position variability increased in the TBI group while it decreased in the control group. This could mean that the TBI group was more vulnerable to accumulated fatigue while sustaining the task, as fatigue has been shown to affect the variability of lateral position (Du et al., 2015). With hindsight, a longer scenario with a greater homogeneity in roadway parameters between time blocks could have been more sensitive to detect time-on-task effects. On a related note, more complex and demanding scenarios could have resulted in greater differentiation of the TBI and control groups on driving simulator measures. Masson and colleagues documented the negative impact of an increased attentional load on the performance of drivers with TBI (Masson et al., 2013). Conversely, it has been shown that an increase in cognitive workload is associated with a decrease in the variability of lateral position (i.e., better vehicle control) in healthy individuals (Cooper, Medeiros-Ward, & Strayer, 2013). The impact of different levels of cognitive workload on driving performance of individuals with TBI has yet to be documented. In the present study, group differences on the number of minor infractions and the performance on a visual attention task were not found. This could be partially related to a lack of statistical power, as the effect size for the mean reaction time on the visual attention task was moderate. Moreover, as it was alluded to previously, it is plausible that this concomitant task, and the driving scenario in general, were too simple to distinguish between groups.

When exploring the relationship between attention and sleep, TMT performance was found to be associated with sleep continuity in the TBI group but not in the control group. Data on the interaction between sleep and cognition in non-sleep disordered TBI samples are scarce, with one study showing poorer attention in individuals with self-reported sleep disturbances

(Bloomfield et al., 2010). In the general population, sleep deprivation is known to affect cognitive performance (Lim & Dinges, 2010). Some studies also suggest an association between slow-wave sleep and attention, although it seems to be mediated by other factors such as age and the presence of insomnia (Pace-Schott & Spencer, 2011). The present study also reveals, in both groups, a significant relationship between poorer performance on the CPT-II and a greater increase of subjective sleepiness. An association between performance and pathological levels of sleepiness has been reported previously in patients with TBI (Castriotta et al., 2007; Wilde et al., 2007). Taken together, these findings might suggest that at least some individuals are more vulnerable to the interaction between sub-optimal sleep or alertness, and reduced attention. In this case, clinicians should pay attention to the impact of previous night's sleep and daytime alertness level when interpreting neuropsychological results. Standard recommendations on strategies to optimize sleep and minimize sleepiness could also be provided. In future studies, associations between cognition and sleep should be further investigated using subjective (i.e., assessed with questionnaires, sleep diaries, clinical interviews) and objective measures of sleep-wake functions. Because PSG is an expensive resource not readily available in most rehabilitation clinical or research settings, research protocols have to consider alternatives that are more easily interpretable, replicable, and applicable, such as actigraphy, which has been used in past studies with TBI samples. The use of mobile phone devices represents an interesting option, as the number of sleep apps is rapidly increasing, but there is a lack of data on their validity and fidelity at this time.

Contrary to some previous reports (Azouvi et al., 2004; Belmont et al., 2009; Riese et al., 1999; Ziino & Ponsford, 2006a, 2006b), there was no significant correlation between neuropsychological or driving simulator performance and subjective fatigue in our sample. However, according to results published previously derived from the same sample, participants with TBI reported greater levels of fatigue compared to their control counterparts on the VAS and other self-reported measures (Beaulieu-Bonneau & Morin, 2012). Moreover, findings from

the CPT-II (i.e. progressive slowing in RT over time in the TBI group but not in the control group) could hint at a fatigue build-up even if it did not correlate with subjective fatigue ratings. Since fatigue is a multidimensional phenomenon and that there is a lack of consensus on its definition and measurement, it is probable that time-on-task fatigability and subjective experience of fatigue are distinct aspects and thus not necessarily related for all individuals.

This study has some methodological limitations to take into consideration. Although participants were well selected and groups were carefully matched, the sample size was small, with insufficient statistical power to detect small to moderate effects. However, this is comparable to what can be found in the literature: in recently published studies with similar objectives and protocols, sample sizes ranged from 3 to 87 participants with TBI (mean of 28.3) (Bloomfield et al., 2010; Castriotta et al., 2007; Chaumet et al., 2008; Cyr et al., 2009; Lengenfelder et al., 2002; Riese et al., 1999; Wilde et al., 2007); and some studies did not include a control group. In the current study, the heterogeneity in clinical characteristics of participants with TBI could have increased the variability on the main outcome measures, therefore reducing the likelihood of finding significant effects. It is possible that the driving simulator scenario might not have been demanding enough to affect performance. It would be interesting in future studies to include multiple driving simulator scenarios varying in duration and task complexity to gain a better understanding of the attention deficits exhibited across individuals with TBI. From a broader perspective, there is also a need to develop standard driving simulator scenarios to facilitate knowledge exchange and comparison between studies. The associations between cognition and sleep reported in this paper were based on only one night of in-lab PSG recording. Although it makes sense from a logistical and experimental standpoint, the first night spent in a laboratory environment is usually considered as an adaptation night and as a result may not be representative of habitual sleep.

Despite the aforementioned methodological caveats, the present study adds to the existing evidence that speed of information processing is still affected several years after

moderate to severe TBI. With regard to the neuropsychological measures, the TMT and CPT-II are widely used and short options that seem to be sensitive to long-term impairments in speed of processing (TMT, CPT-II) and sustained attention (CPT-II). As for the ACT, since the pattern of results was unexpected and contrary to previous report, it might not be reliable enough to warrant its use in standard clinical context. The findings derived from the driving simulator task suggest that attention problems are not only observable in standardized paper-and-pencil or computerized cognitive tests, but also on complex, interactive, and more ecologically valid tools. Clinicians should be cautious when evaluating the driving capacities of patients with deficits in speed of processing, and driving simulator scenarios should be developed and used to assist decision-making. The study also underlined that attention appears to be associated with sleep-wake functions, suggesting that patients, clinicians, and researchers alike should take notice of this interaction, especially given the fact that individuals with TBI are vulnerable to sleep-wake disturbances. For instance, cognitive assessment, especially for attention functions, could be spread out over several sessions to monitor attention fluctuations according to the quality and quantity of previous sleep, daytime sleepiness, and the timing of the assessment relative to the circadian clock. In the future, scientists should find innovative ways to improve our understanding of the interface between cognition, sleep-wake-functions, and fatigue following TBI.

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Table 1 – Characteristics of participants by group

Variables (unit, range)	TBI (*N* = 22) M (SD)	Control (*N* = 22) M (SD)	Comparison
Age (years, 18-59)	37.46 (13.26)	36.96 (14.08)	$t(42) = 0.12$, $p = 0.90$
Education (years, 9-18)	12.41 (2.46)	13.09 (2.41)	$t(42) = -0.93$, $p = 0.36$
Driving experience (months, 5-502) [a]	208.27 (156.93)	235.23 (163.20)	$t(42) = -0.56$, $p = 0.58$
Time since TBI (months, 13-141)	53.00 (37.08)		
Initial GCS score (3-15)	7.23 (3.60)		
Duration of coma (days, 0-30) [b]	9.76 (9.47)		
Duration of PTA (days, 7-77) [c]	25.20 (15.71)		
	n (%)	*n* (%)	
Gender (women)	5 (22.7%)	5 (22.7%)	χ^2 (1, $N = 44$) = 0.00, $p = 1.00$
Occupation (working/studying)	7 (31.8%)	20 (90.9%)	χ^2 (1, $N = 44$) = 16.20, $p < 0.001$
Long-term medical disability	13 (59.1%)	0 (0%)	χ^2 (1, $N = 44$) = 18.45, $p < 0.001$
Current driver's license	18 (81.8%)	22 (100%)	χ^2 (1, $N = 44$) = 4.40, $p = 0.04$
Psychotropic medication use [d]	11 (50.0%)	4 (18.2%)	χ^2 (1, $N = 44$) = 4.96, $p = 0.03$
TBI severity			
Moderate	3 (13.6%)		
Moderate-severe	2 (9.1%)		
Severe	17 (77.3%)		
TBI cause			
Assault	1 (4.6%)		
Fall	2 (9.1%)		
Motor vehicle – traffic	18 (81.8%)		
Struck by/against	1 (4.6%)		

Abbreviations: GCS = Glasgow Coma Scale; PTA = posttraumatic amnesia; TBI = traumatic brain injury.
[a] For participants with TBI, the post-TBI license revocation period was excluded from the calculation. [b] Data available for 17/22 participants with TBI. [c] Data available for 20/22 participants with TBI. [d] Two participants with TBI used two psychotropic medications (total: 13 medications used by 11 participants).

Table 2 – Between-group comparisons on neuropsychological measures

Variables (unit, total range)	TBI (*N* = 22) M (SD)	Control (*N* = 22) M (SD)	One-way ANOVAs (if significant MANOVA)	*d*
TMT				
1: Visual Scanning (s, 10-61)	24.91 (10.12)	18.91 (4.70)	F (1, 42) = 6.36, p = 0.02	0.76
2: Number Sequencing (s, 15-67)	36.59 (14.17)	27.77 (9.53)	F (1, 42) = 5.87, p = 0.02	0.73
3: Letter Sequencing (s, 17-80)	35.91 (15.96)	27.86 (13.92)	F (1, 42) = 3.18, p = 0.08	0.54
4: Switching (s, 36-128)	77.18 (26.83)	62.32 (18.68)	F (1, 42) = 4.55, p = 0.04	0.64
5: Motor Speed (s, 11-50)	25.77 (9.89)	19.55 (6.52)	F (1, 42) = 6.08, p = 0.02	0.74
Contrast TMT-4vs1 (ratio, 0.51-5.36)	2.25 (1.00)	2.39 (0.96)	F (1, 42) = 0.21, p = 0.65	0.14
Contrast TMT-4vs2 (ratio, 0.37-2.72)	1.18 (0.57)	1.35 (0.61)	F (1, 42) = 0.98, p = 0.33	0.29
Contrast TMT-4vs3 (ratio, 0.29-3.23)	1.30 (0.71)	1.38 (0.51)	F (1, 42) = 0.19, p = 0.67	0.13
Contrast TMT-4vs4 (ratio, 0.46-7.09)	2.24 (1.30)	2.53 (1.65)	F (1, 42) = 0.43, p = 0.51	0.20
ACT				
9-s interval (# correct, 4-15)	9.00 (3.28)	11.36 (2.46)	F (1, 42) = 7.31, p = 0.01	0.81
18-s interval (# correct, 5-15)	9.09 (2.56)	10.09 (3.05)	F (1, 42) = 1.39, p = 0.25	0.36
36-s interval (# correct, 1-14)	7.68 (3.43)	7.95 (3.43)	F (1, 42) = 0.07, p = 0.79	0.08
CPT-II				
Omissions (#, 0-14)	1.91 (3.24)	1.95 (3.24)	F (1, 42) = 0.002, p = 0.96	0.01
Commissions (#, 1-32)	11.77 (8.08)	12.18 (6.93)	F (1, 42) = 0.03, p = 0.86	0.05
Hit RT (ms, 306.61-589.98)	420.16 (64.69)	377.25 (68.81)	F (1, 42) = 4.54, p = 0.04	0.64
Hit RT SE (ms, 2.45-9.05)	5.88 (1.86)	4.35 (1.03)	F (1, 42) = 11.36, p < 0.01	1.02
RT block change (slope, -0.03-0.05)	0.01 (0.02)	-0.01 (0.02)	F (1, 42) = 7.08, p = 0.01	0.87
Driving simulator task				
Minor infractions (#, 0-9)	1.77 (1.93)	1.32 (1.59)		0.31
Hit RT (s, 0.99-3.86)	1.80 (0.68)	1.46 (0.27)		0.66
Error rate (%, 0-70)	10.10 (15.97)	5.03 (11.54)		0.36

Abbreviations: ACT = Auditory Consonant Trigrams; CPT-II = Continuous Performance Test II; *d* = measure of effect size (Cohen's *d*); RT = reaction time; SE = standard error; TBI = traumatic brain injury; TMT = Trail Making Test.

Figure captions

Figure 1 – Procedure of the second visit to the sleep centre. ACT = Auditory Consonant Trigrams; CPT-II = Continuous Performance Test II; MWT = Maintenance of Wakefulness Test; PSG = polysomnography; TMT = Trail Making Test; VAS = visual analogue scales.

Figure 2. – Results of the variability of vehicle lateral position on the driving simulator task over time for TBI and control groups. Data were weighted for distance travelled within each 9000-m block. Error bars represent standard errors. TBI = traumatic brain injury.

Figure 1.

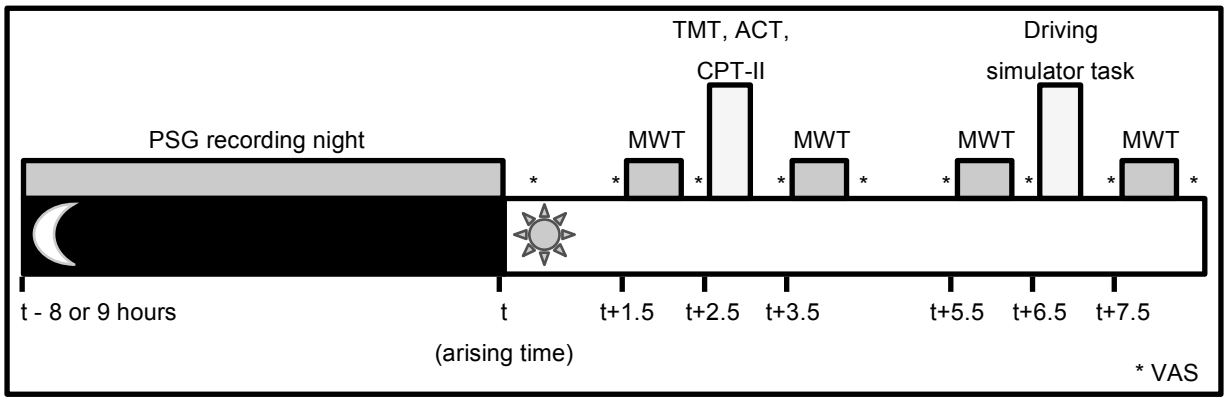
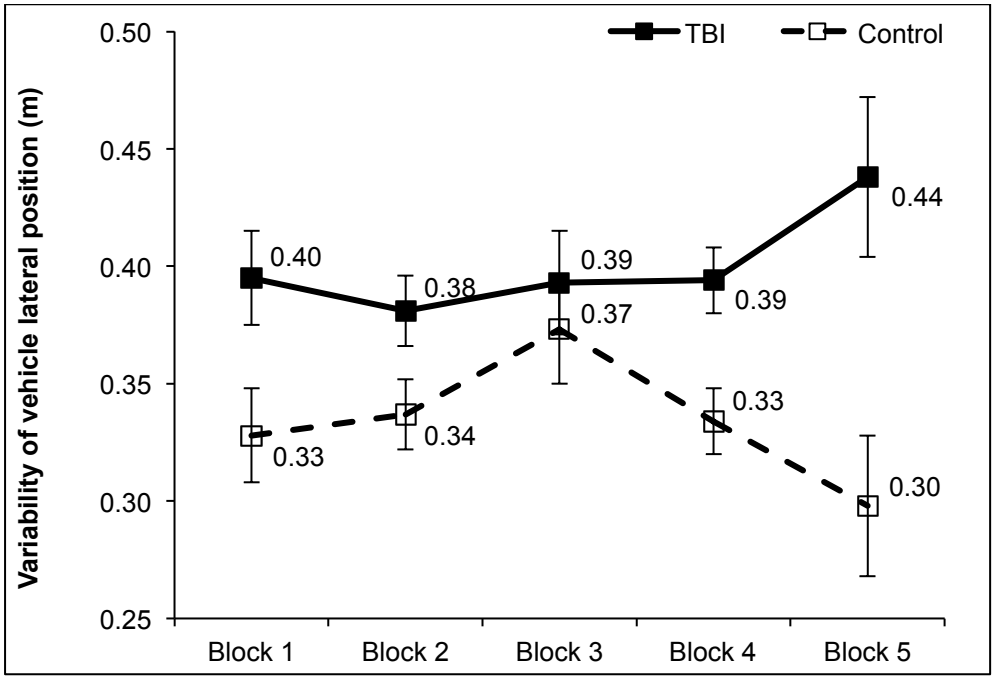

TMT, ACT,
CPT-II
Driving
simulator task
PSG recording night
MWT
MWT
MWT
MWT
t - 8 or 9 hours
t
(arising time)
t+1.5
t+2.5
t+3.5
t+5.5
t+6.5
t+7.5
* VAS

Figure 2.


TBI
Control
Variability of vehicle lateral position (m)
0.50
0.45
0.40
0.35
0.30
0.25
0.40
0.38
0.39
0.39
0.44
0.33
0.34
0.37
0.33
0.30
Block 1
Block 2
Block 3
Block 4
Block 5