Graduate Thesis

Traumatic Brain Injury Assessment: Sensitivity and Specificity with Inclusion of QEEG Parameters

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Abstract

Addressing issues with sensitivity and specificity in TBI assessment this study compared the performance on neuropsychological tests and results from qEEG assessment between a heterogeneous TBI (N=20) group and a matched normal control group (N=20). The TBI group was performed worse on all measures. Significant differences in performance were found in the domains of information processing speed and executive function. Effect sizes of these differences were large. This was also true for the amplitude of the qEEG parameter P3NoGo along with P3Go latency and theta power in the temporal and frontal lobes. Binary logistic regression revealed higher sensitivity and specificity when combining neuropsychological tests and qEEG parameters, suggesting qEEG parameters in combination with neuropsychological tests to be good assets in TBI assessment.

Keywords: TBI, assessment, neuropsychology, qEEG, sensitivity, specificity

Every year tens of thousands of persons acquire traumatic brain injury (TBI) worldwide causing deficits and disability in cognitive, emotional and social functioning (Maas, Stocchetti, & Bullock, 2008). The incidence rates of TBI reported varies between countries and there is no general consensus on how to count incidents (Bruns & Hauser, 2003). For the European Union (Tagliaferri, Compagnone, Korsic, Servade, & Kraus, 2006) reviewed literature and found an aggregate incidence of TBI at approximately 235 per 100 000, including fatalities. In Norway, (Ingebrigtsen, Mortensen, & Romner, 1998) found the incidence rate to be 157 / 100.000 with a male-female ratio of 1.7:1.0. The main causes were falls (62 %), traffic accidents (21 %) and assaults (7 %). In the Stavanger region, 2003, (Heskestad, Baardsen, Helseth, Romner, Waterloo, & Ingebrigtsen, 2009) found the incidence rate to be 157 / 100.000 with a male-female ratio of 1.7:1.0. The main causes were falls (51 %), traffic accidents (21 %) and assaults (14 %). In Oslo between 2005 and 2006, the incidence rate was found to be 83.3 / 100.000 with a male-female ratio of 1.8:1.0. The main causes were falls (51 %) and transport accidents (29.7 %) (Andelic, Sigurdardottir, Brunborg, & Roe, 2008).

TBI affects patients' cognitive (Temkin, Corrigan, Dikmen, & Machamer, 2009) and social (Dikmen, Corrigan, Levin, Machamer, Stiers, & Weisskopf, 2009) capabilities making many dependent on a variety of coordinated health and social services. Estimation of injury severity, predictions of patient outcome and feasibility of different rehabilitation initiatives relies heavily on medical imaging (Ghajar, 2000) and neuropsychological assessment and observations (Patry & Mateer, 2006). Recent research by Skandsen, Finnanger, Andersson, Lydersen, Brunner, & Vik, (2010) have shown that impairments in cognitive functioning vary and often are difficult to assess because of a high rate of normal test scores within the patient population. That is despite problems maintaining working status and social functioning (Mazaux et al., 1997). Hartikainen et al., (2010) argues that the structured testing environment

created to assess distinct functions may not be sensitive to the problems experienced in everyday situations which affect patient total functioning and quality of life. This can lead to mistreatment or no treatment or rehabilitation at all. A person who doesn't show any objective signs of disability may be considered querimonious and rejected. It has been suggested that advanced medical imaging techniques like DTI and fMRI may be sensitive to the physical effects of TBI and correlated to behavioral measures (Kou, et al., 2010, andIngebrigtsen, Rise, Wester, Romner, & Kock-Jensen, 2000). This is also reported for quantitative electroencephalography (qEEG) measures (Reinvang, 1999, and Thornton & Carmody, 2009) and qEEG has been viewed as a possible supplement to neuropsychological tests in TBI assessment (Mazzini, 2004, and Duff, 2004).

The aim of the study was to investigate how well neuropsychological tests and qEEG parameters differentiate TBI patients from normal controls, and whether the inclusion of qEEG in TBI assessment could increase the sensitivity and specificity of assessment.

Causes and Effects

TBI refers to the physical effects to the brain from the application of external physical force, including acceleration/deceleration forces. Contact forces working on the head (e.g. smashing the head into the pavement) may accelerate the brain within the skull causing tissue bruising near the bony structures of the skull on both the point of impact and on the contralateral side. This is often referred to as coup and counter coup lesions (Gaetz, 2004). Bruising in brain tissue is also apparent without any direct blows to the head, but from just mere acceleration or deceleration (A/D) forces (e.g. traffic accidents). The frontal and temporal poles are most vulnerable to these forces because their cortex rest on rough surfaces of the skull. With increasing force deeper structures like the basal ganglia, corpus callosum, and the brain stem may also be affected. The movement of the brain within the skull not only

produces bruising but also shearing and tearing of delicate tissues. This includes both blood vessels and nerve fibers creating intracranial hemorrhages and diffuse axonal injury (DAI) (Gaetz, 2004). DAI is often observed in the grey-white matter junction within the frontal and temporal lobes, in the corpus callosum and especially in its dorsal part, the splenium (Gentry, 1994). With increasing force DAI is also observed in the dorsolateral part of the midbrain, in the rostral part of the pons, and in the brain stem (Parizel, et al., 1998). While contusions often are associated with specific and localizable changes in brain functioning, axonal injury contributes to a somewhat diffuse change (Scheid, Walther, Guthke, Preul, & Yves von Cramon, 2006).These are mainly primary injuries which are related to the forces applied to the brain. Another group of injuries are referred to as secondary injuries. These include edema, metabolic changes and altered cerebral blood flow. Edema may lead to ischemic damage and increased intracranial pressure which can be fatal if not treated and controlled (Moppett, 2007). There is also a heightened risk of infection, especially if the skull and dura is breached (Hannay, Howieson, Loring, Fischer, & Lezak, 2004). On the cellular level a cascade of neurochemical and neurometabolic events are initiated. Disruption of the cell membrane of the neuron and stretching of axons causes a chaotic flux of ions through the membrane which again cause the neuron to release large amounts of excitatory amino acids (Farkas, Lifshitz, & Povlishock, 2006, and Katayama, Becker, Tamura et al., 1990). With the resulting massive efflux of potassium the ATP driven ionic pumps increase their activity causing higher energy demands. High ATP consumption leads to hyperglycolysis and changed metabolism. Axonal events include calcium influx which may lead to axonal swelling and in serious cases axotomy (Maxwell, McCreath, Graham, & Gennarelli, 1995).

To summate, a common pattern in TBI is a primary injury caused by the mere contact forces and inertial forces causing contusions, lacerations, diffuse axonal injury, and hematoma. This is often followed by a secondary injury risking further damage to brain tissue

by elevated intracranial pressure (ICP), edema, hypoxia, ischemia, pyrexia, infections and a cascade of intracellular processes. The frontal and temporal lobes are most susceptible to damage and with increasing force may deeper structures also be affected and the risk of DAI increase.

Cognitive, Emotional and Behavioral Consequences

The mentioned vulnerable regions, the frontal and temporal lobes, are involved in important perceptual, cognitive and emotional processing (Fork et al., 2005). Symptoms of damage to the ventral frontal cortices are behavioral disinhibition, emotional dysregulation and irritability while damage to the anterior cingulate cortex often results in apathy. Patients with damage to the inferolateral prefrontal cortex often show working memory impairments and impairment in executive function if the dorsolateral prefrontal cortex is affected (Silver, McAllister, & Arciniegas, 2009). Executive function is an umbrella term for complex cognition which includes control of attention, memory, language, motor planning, along with abstraction and judgment. Temporal lobes are important structures for memory and emotion. Damage to the anterior (polar) temporal cortex may result in a wide range of social and emotional disturbances along with a disturbance in semantic memory. Damage to the enthorinal and hippocampal structures and neural pathways connecting these structures to others commonly result in impaired declarative memory and working memory (Tate & Bigler, 2000, and Smith, Lowenstein, Gennarelli, & McIntosh, 1994). If the amygdale is affected one might observe affective placidity or alternatively anxiety (Silver et al., 2009). Damage to the midbrain can disturb the reticular activation system responsible for conscious experience (Parvizi & Damasio, 2001).It may also may cause deficits in nuclei integrating visual and sensory information and cause movement disabilities like tremor and rigidity (Hannay et al., 2004). Lesions in the midbrain have also been associated with verbal memory problems (Holli, et al., 2010).

General Assessment and Research

TBI assessment is multifaceted and consists of several key elements, often repeated at different times during the course of illness and recovery. In the acute phase measures like duration of loss of consciousness (LOC), duration of an altered mental state of confusion and disorientation called post-traumatic amnesia (PTA),and the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) score are used to predict injury severity and outcome (Hannay et al., 2004). The Glasgow coma scale comprises three tests of eye, verbal, and motor responses and scores range from 3 to 15 and injury severity is commonly classified into categories of mild, moderate and severe with mild defined as GCS 13-15, PTA <1 day, LOC < 30 minutes, and moderate GCS 9-12, PTA 1-7 days, LOC 0.5-24 hours and finally severe GCS 3-8, PTA > 7 days, LOC > 24 hours (Ghajar, 2000, andHannay et al., 2004). The Scandinavian Neurotrauma Committee (SNC) (Ingebrigtsen et al., 2000) suggests a separation into minimal (GCS 15, no LOC); mild (GCS 14-15, short <5min LOC or PTA); moderate (GCS 9-13, >5min LOC or PTA); severe (GCS 3-8). This classification is stricter and justified by research showing exponentially increasing CT anomalies with decreasing GCS score (Culotta, Sementill, Gerold, & Watts, 1996). With the latter classification a GCS of 13 would yield a moderate TBI. The use of this classification is increasing, especially in the field of neurosurgery (Maas, Stocchetti, & Bullock, 2008).

Imaging techniques like computer tomography (CT) and magnetic resonance imaging (MRI) offer important information following accidents. CT is a highly used and valuable tool for diagnosis. CT is sensitive to skull and facial bone fractures using a bone window and sensitive to hematomas and raised ICP using a soft tissue or brain window (Ingebrigtsen et al., 2000). CT can enable the clinician to rapidly assess if the patient is in need of urgent neurosurgery. Patients with a GCS score of 15 rarely show any CT abnormalities and it is also

rare for patients with no LOC or just brief PTA to show any abnormalities on immediate CT scans (Ingebrigtsen et al., 2000).

MRI has an excellent soft-tissue contrast compared to CT and is more sensitive in locating cortical contusions, diffuse axonal injury (DAI) and brain stem lesions (Gentry, Godersky, Thompson, & V.D., 1988, and Skandsen, 2010). Although MRI has become more accessible in the recent years it is still a costly procedure and is difficult to use on patients dependent on machines sensitive to magnetic fields. In addition to CT and MRI there are other methods of brain imaging like positron emission topography (PET) where the patient inhales radioactive glucose and single photon emission computer topography (SPECT) where a radioactive compound is injected into the blood stream. These methods are usually not included in regular TBI assessment (Belanger, Vanderploeg, Curtiss, & Warden, 2007).

Neuropsychological assessments are important in order to estimate current functioning, prognostication, development of treatment plans and rehabilitation (Taylor, Livingston, & Kreutzer, 2007). It often plays a significant role in forensic settings and with insurance or disability pension payouts (Bigler & Brooks, 2009). Although imaging techniques like MRI and CT may be sensitive to TBI, Patry & Mateer, (2006) argues that the frequent coexistence of focal as well as diffuse injuries to brain tissue may preclude inferences about deficits in certain cognitive domains. By employing a comprehensive neuropsychological assessment clinicians may ascertain that the majority of important mental functions are probed.

The neuropsychological assessment of TBI patients is diverse and varies with regard to many different variables (e.g. age, severity, location, availability of tests and equipment) and what problems that are described by the patient or others close to the patient. Patients with mild TBI often report attentional deficits and complaints about poor short-term memory (van Zomeren & Brouwer, 1994, and Sohlberg & Mateer, 2001), even one year after injury

(Rickels, von Wild, & Wenzlaff, 2010). However, the symptoms are most prominent in the acute phase and research has shown that most patients do not have lasting problems (Hannay et al., 2004). Moderate TBI patients differ from mild TBI patients in that they exhibit more distinct cognitive, emotional, and behavioral symptoms, often related to the increased incidence of frontal and temporal bruising and axonal injuries (Hannay, et al., 2004). Severe TBI can have an enormous impact on almost all aspects of life even decades after injury. Patients with severe TBI have difficulties returning to work. Those who do return to work often only function in highly supportive settings (Skandsen, Lund, Fredriksli, & Vik, 2008). Family and social function may be low and patients may not be able to care for themselves. There is also an increased incidence of psychiatric disorders and suicide in patients with moderate and severe TBI (Rogers & Read, 2007).

Based on the locations most vulnerable to injury some domains of neuropsychological dysfunction and tests thought to measure these are more documented and used than others. The most common sequelae of TBI are dysfunctions in the neuropsychological domains of attention and processing speed, executive function and learning and memory. In addition, changes on measures of intelligence, emotionality and personality are often observed (Patry & Mateer, 2006).

Although having names and constructs for the reported dysfunctions, choosing tests to measure them is a challenge. As an example there is no fully agreed-upon definition of the construct attention and attention is thought to consist of several mental operations like selective, focused, divided attention, attention span and sustained attention, and speed of processing (Bate, Mathias, & Crawford, 2001). Because of the close relationship between attention and processing speed it may be difficult to know whether an impaired attention score reflects a true attentional deficit or reduced processing speed (Cossa & Fabiani, 1999). To date no single test might tap into all aspects of attention. As a consequence

neuropsychologists typically measure aspects of attention and processing speed using several tests. Frequently used measures that show group differences between patients and controls on processing speed are the Color-Word Interference Test and Trail Making Test (Skandsen, Finnanger, Andersson, Lydersen, Brunner, & Vik, 2010).With regard to sustained attention Riccio, Reynolds, Lowe, & Moore, (2002) found the Conners Continuous Performance Test (CPT) to be sensitive to the focal and diffuse damages in TBI. Loken, Thornton, Otto, & Long, (1995) found deficits in sustained attention and vigilance with the CPT in patients tested two months post-injury. Attention span is widely measured with the digit-symbol subtest of WAIS and TBI patients are found to have reduced attention span in the acute and sub-acute phases (Kersel, Marsh, Havill, & Sleigh, 2001).

Cognitive functions like learning and memory are important in everyday functioning and are important to assess in all patient groups, including TBI patients. Memory is typically evaluated separately in verbal and visual modalities with a design allowing testing of encoding/registration, storage/rehearsal, and retrieval as described in the three-stage model of (Bauer, 1993, and Blachstein, 1993). Verbal memory is commonly assessed with the California Verbal Learning Test (CVLT). Using the verbal learning factor derived from patient performance on five consecutive learning trials, Gardner & Vrbancic, (1998) could successfully discriminate moderate/severe TBI patients from normal controls with an 84-88 per cent accuracy rate. Regarding visual memory, one test, the continuous visual memory test (CVMT) has proved useful, correctly classifying up to 75% of patients (Strong & Donders, 2008). Executive functions are difficult to assess directly because of their wide definition. As a consequence neuropsychologists typically use a battery of tests in order to tap this domain. Often used are the Wisconsin Card Sorting Task, the Verbal fluency test, the inhibition and switching conditions of the Trail making test, and the color word interference test. Motor

function may also be affected by focal and diffuse TBI. Fine motor function as measured with the Grooved Pegboard test shows some sensitivity to TBI (Skandsen et al., 2010).

Although several studies presented above demonstrate high discriminative ability of some tests, Reitan & Wolfson, (2008) question neuropsychological tests ability to produce unequivocal evidence of brain damage. Recent research by Skandsen,(2010) has found neuropsychological tests to demonstrate low sensitivity to TBI and reported cognitive complaints. It was further found that speed dependent tests like TMT and CWIT showed the largest effect sizes and that tests of working memory like digit span backwards and letter-number sequencing were insensitive to TBI. The same was reported for tests of visual memory measured with the CVMT and for attention measured with CPT-II. Skandsen also found that despite these seemingly normal test scores, the patients reported significant cognitive complaints on the extended Glasgow Outcome Scale (GOSE).From self-report studies on TBI patients (Draper & Ponsford, 2009) found problems with attention and concentration to be frequently reported as problematic. Some research (Ruff, 2009) states that it is in cases of damage affecting these cognitive functions neuropsychological tests have their biggest limitations.

QEEG assessment and research

While neuropsychological tests may measure differences in behavioral performance on different mental and motor tasks, modern quantitative EEG (qEEG) techniques have the potential to expand our knowledge of differences in neural processing in TBI patients by comparing them to normal controls (Gaetz & Bernstein, 2001). Research on qEEG parameters as sensitive indicators of disorders like ADHD and schizophrenia has already been published (Mueller, Candrian, Kropotov, & Baschera, 2010; Snyder, Quintana, Sexson, Knott, Haque, & Reynolds, 2008, and Galderisi, Mucc, Volpe, & Boutros, 2009) giving the clinician

indications for diagnosis and treatment. Brain activity as recorded by the EEG electrodes is important in communication between and within brain structures (Colgin, et al., 2009) .Plotting this data will give a good picture of the amplitudes and trends in activity like spikes and bursts, but it can be difficult to quantify the magnitude of different frequencies in the data since all frequencies are represented by one single line. By quantifying the EEG signals into a time-series matrix of repeated measurements of electrode potentials (qEEG), researchers may use statistical and data mining tools to objectively analyze and compare the electrical (brain) activity within and between individuals and groups of individuals.

There is a well of possible parameters to extract from a single qEEG recording. In TBI research there is a wide use of event-related potentials (ERPs) and frequency spectrum magnitudes (spectra) .ERPs are recorded as time-series data linked to a specific event presented to the patient (i.e. a Go/NoGo task or the oddball paradigm). Because it is measured in time-series, ERPs have excellent time resolution and provides the researcher with a window into the neural activity associated with stimuli perception and processing. By averaging many trials, activity associated with processing of the event is enhanced while random noise is averaged out. ERPs are named after their polarity and latency from a baseline set at stimulus onset (e.g. N100 is the negative potential after approximately 100ms) or based on polarity and number of appearance (e.g. P3 is the third positive potential after stimulus onset). Actual latencies may vary greatly depending on testing condition and population. ERPs loose frequency resolution and research has established connections between the magnitude of different frequencies and mental operations(e.g. Laufs, et al., 2003).Applying frequency spectrum analysis to the qEEG data transforms the data from the time domain to the frequency domain. By the use of Fourier transform the waves in the EEG signal is converted to sums of sinusoidal waves with different frequencies where the magnitude of each sinusoid can be represented in a frequency power spectrum (Sanei & Chambers, 2007). The

spectrum consists of different frequency bands defined as delta (<4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (12-30 Hz), gamma (>30 Hz) (Handy, 2005).

For TBI patients prior studies has shown changes in EEG activity in the frontal and temporal lobes (Thatcher, Biver, McAlaster, & Salazar, 1998; Thornton & Carmody, 2009, and Duff, 2004). These changes correlate with injury severity and neuropsychological status (Wallace, Wagner, Wagner, & McDeavitt, 2001, and Alvarez, et al., 2003). ERP changes are associated with changed states in cognitive functions. Early ERPs (e.g. the P50) has been associated with attention and memory (Arciniegas & Topkoff, 2004). Another ERP which has been exhaustively studied in relation to TBI is the P300 (also known as P3) which has been linked to a wide range of cognitive processes like attention, working memory, and stimuli detection (Polish, 2007). The amplitude of the P300 has been thought to indicate utilization of cortical attentional resources and larger amplitudes have been found to correlate with better cognitive performance (Lew et al., 2005, and Lew, Thomander, Gray, & Poole, 2007). A common finding in the P300 ERPs is a reduction in amplitude and increase in latency following injury (Larson, Kaufman, & Perlstein, 2009). These changes also correlate with behavioral and neuropsychological measures (Potter & Barrett, 1999; Reinvang, 1999; Solbakk, Reinvang, & Andersson, 2002, and Solbakk, Reinvang, Svebak, Nielsen, & Sundet, 2005). Especially one variant of the P300 ERP, namely the P3NoGo which emerges in a situation where the subject is exposed to ambiguous information and is forced to make a choice between two actions (conflict processing or top-down attentional control) has been proposed as sensitive to TBI. Roche, Docree, Garavan, and Robertson, (2004) showed complete absence of this component in TBI patients compared to normal controls. On the novelty P3a ERP which emerges in situations where novel stimuli are presented Potter and Barrett (1999) found increased latency in association with attention and memory problems. The increase of latency was attributed to slowed processing in frontal regions.

Research using frequency spectrum has shown changes in TBI patients compared to normal controls. Tebano, et al., (1988) found that mild TBI patients had a shift toward lower frequencies in peak alpha rhythm. Fenton, (1996) linked increased theta activity in frontal and temporal lobes to brain stem injury and cognitive symptoms and complaints. In the eyes closed condition (Thornton & Carmody, 2009) also reported an increase in theta activity in TBI patients. Various qEEG parameters like coherence, frequency and phase was used by Thatcher, Walker, Gerson, & Geisler, (1989) in order to make discriminant function to seperate qEEG patterns between patients with mild TBI and age-matched controls and reported an overall classification accuracy of 94,8%.

In reviews by Gaetz & Bernstein, (2001) and Duff, (2004), are ERP and frequency specrum measures suggested as promising qEEG parameters to detecting the effects of TBI to the activity of the brain. Because of the vast consequences TBI may have for both the patient and his/her social network and the cost this incurs on society it is of great importance to have sensitive and specific assessment tools. This is important to ensure good patient treatment and rehabilitation. This includes knowledge of what happens on a physical and biological level as well as the psychological and behavioral level. Lew, Lee, Pan, & Date, (2004), and Mazzini, (2004) suggested inclusion of qEEG measures in the assessment of TBI patients as an addition to neuropsychological tests.

The present study

The aim of this study was to investigate which neuropsychological tests and qEEG parameters that could differentiate between TBI patients and normal controls. In addition, it was investigated whether qEEG parameters combined with neuropsychological tests could give higher sensitivity and specificity to TBI assessment.

Method

The Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services (NSD) approved the study and written consent was obtained from the patients and from the parents of patients younger than 16 years. Data is collected trough the Head injury project at St.Olavs Hospital, Trondheim University Hospital. For more information on the Head Injury project see Skandsen (2010).

Participants

Twenty-two patients (8 women, 12 men, M_{age} = 30.5 years, age range: 14-63 years, $M_{education}$= 12.5 years) admitted to the department of neurosurgery, St. Olavs Hospital, Trondheim University Hospital, Norway participated in the study. Neuropsychological and EEG assessment was conducted at 3 months post injury. Patients had no ongoing PTA or critical neurological or psychiatric diagnosed conditions at the time of assessment. The control group consisted of 22 healthy persons, matched for age, sex and education (9 women, 13 men, M_{age} = 30.8 years, age range: 14-64 years, $M_{education}$= 12.8 years). They were recruited via advertisements, among family and friends of patients with head injury and among acquaintances of researchers and staff.

Injury and outcome variables

The injury-related variables were; mechanism of injury (MOI), GCS score, and days of PTA. The patients were also questioned regarding any pre-morbid conditions. GCS was scored according to procedures described in Ingebrigtsen et al., (2000) with injury being mild if GCS ≥ 14, moderate at GCS score 9-13 and severe at GCS score ≤ 8. PTA was rated by the department resident. Global functioning was assessed at 6 and 12 months post injury with the Glasgow Outcome Scale Extended (GOSE). GOSE score ≤ 7 denotes presence of head injury-related disability or complaints to a degree that they affect daily life (Skandsen et al., 2010).

Procedure for neuropsychological testing and scoring

Assessments were performed at minimum 83 and maximum 133 days after injury *M* = 98 days after injury. Testing was performed by test technicians, master level students and certified psychologists at St. Olavs University Hospital. Raw scores were converted to standard scores as provided by the manufacturers of the tests.

Neuropsychological measures

Patients and controls were tested with a comprehensive neuropsychological battery. This paper focuses on neuropsychological tests that tap functions known to be affected by TBI. These are: Grooved Pegboard (Bryden, Roy, & Bryden, 1998) and Trail making test (TMT) condition 5 from the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) for motor function, Color Word Interference Test (CWIT) conditions 1 (color naming) and 2 (word reading), and TMT condition 1 (visual scanning), 2 (numbers), and 3 (letters) from the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) for information processing speed, Conners' Continuous Performance Test II (CPT-II) (Conners & Staff, 2000) for attention and vigilance, Continuous Visual Memory Test (CVMT) (Trahan & Larrabee, 1988) for visual learning and memory, California Verbal Learning Test II(CVLT) (Delis, Kramer, Kaplan, & Ober, 2000) for verbal learning and memory, Letter-Number Sequencing and Digit Span backwards from the Wechlers Memory Scale (WMS-III) (Wechsler, 1997) for working memory, and Verbal Fluency Test from Delis Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001), TMT condition 4 (category) and CWIT inhibition and inhibition/switching for executive functions.

Procedure for qEEG recording

Testing was performed by master level students and psychologists trained in qEEG recording. QEEG was recorded using a Mitsar 201 PC-controlled 19-channel (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz and Pz) system. Tin electrodes were placed according to the international 10-20 system (Jurcak, Tsuzuki, & Dan, 2007) using a standardized electrode cap. The letter F refers to frontal, C to central, P to parietal, T to temporal, and O to occipital. Left hemisphere locations are indicated by odd numbers and right hemisphere locations by even numbers. Central midline locations are indicated by the letter z. Signals were referenced to clip electrodes placed at both ears and a ground electrode at Fpz. Signals between 0,5 and 50 Hz were digitized at a sampling rate of 250 Hz (sample interval = 4 ms). Digitized data was recorded and quantified by the WinEEG software. Recordings were cleaned in an average reference montage with exclusion of general high amplitude (>100 μV) and fast and slow high amplitude activity (>35 μV at 20-35 Hz and >50 μV at 0-1 Hz). Eye blink artifacts were corrected by zeroing eye blink independent components (as done in Tereshchenko, Ponomarev, Kropotov, & Müller, 2009). All qEEG files were manually inspected to verify artifact removal.

Subjects were seated in a comfortable chair placed 1.5 meters in front of a 17 inch LCD screen. The behavioral task consisted of a 3 minutes eyes open and a 3 minutes eyes closed resting state condition. Subjects then performed the 22 minutes, 400 trials visual continuous performance task (vCPT) run on a slave computer by the Psytask (Mitsar Ltd.) software. The vCPT is a modified two-stimulus Go/NoGo test with four conditions; GO (animal-animal), NoGo (animal – plant), Ignore (plant – plant), and Novelty (plant – human + sound). Subjects are instructed to respond as fast and accurate as possible to the Go trials by clicking on a computer mouse. The trial conditions and stimuli examples are presented in

figure 1. For a more detailed description of the paradigm, see (Mueller, Candrian, Kropotov, & Baschera, 2010).

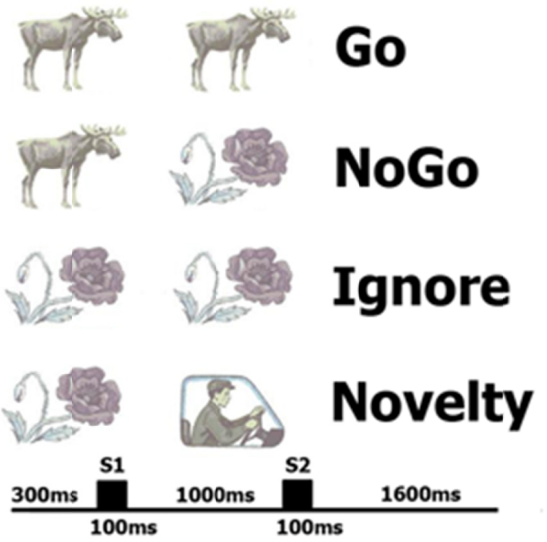

Figure 1: vCPT conditions and timing.

QEEG measures and feature extraction

The four VCPT trial conditions were sorted post-experimentally and individual behavioral results and ERPs were acquired with the WinEEG software. Trials were scored as an error when there was a response on a NoGo trial (commission error), no response on a Go trial (omission error) and on any trial on which more than one response was made. Individual mean reaction time (RT) was calculated based on valid Go trials with response > 200 ms and < 1000ms after second stimulus onset to exclude anticipations and late responses to previous trial. The standard error of the mean reaction time was obtained by dividing the standard deviation by the square root of number of valid Go trials ($SE = \frac{sd}{\sqrt{n}}$).Notice that the *SE* is sensitive to the number of valid trials.

To extract ERPs, channel potentials for trials in each condition were averaged with amplitude baseline set at second stimulus onset. Peaks were detected and registered manually

within a specified post-second stimulus latency range at a specified site (100-300ms at Fz for P3a (novelty trials), 200–600 ms at Cz for P3 (NoGo trials), and 200–600 ms at Pz for P3b (Go trials). ERP latencies were recorded as the time from second stimuli onset to the Fz, Cz, and Pz peaks.

Statistical analysis

Variables used in analyses were checked for normality by inspection of Q-Q plots and by the Shapiro-Wilk test (alpha set to 0.05). For normally distributed variables the central tendency were reported as arithmetic mean with standard deviation. The Student *T*-test was used for testing for differences between the groups with equal variance assumed unless Levene's test showed significant deviation from equal variance. Unequal variance was controlled for by adjusting the *df*. Effect sizes were calculated as Cohen's *d* with pooled variance $d_{pooled} = \frac{Mean_{TBI} - Mean_{Control}}{SD_{pooled}}$). For non-normally distributed variables the central tendency was reported as median with inter-quartile range (IQR). The Mann-Whitney *U*-test was used to test for between group differences. Effect sizes were calculated by dividing the groups median difference with the pooled IQR times 0.75 ($ES_{IQR} = \frac{Median_{TBI} - Median_{Control}}{IQR_{pooled} x\ 0.75}$). Initial alpha was set to 0.05. Bonferroni correction was used to control for multiple comparisons within each category of neuropsychological test. For the spectral measures a $p \leq 0.01$ was considered significant to avoid losing power.

In order to investigate how addition of qEEG parameters to TBI assessment may affect sensitivity and specificity binary logistic regression was applied. Group membership was the dependent dummy coded binary variable with positive value indicating TBI group membership. The maximum numbers of covariates were limited to one fifth of the number of events in the smallest group making four in this study (Vittinghoff & McCulloch, 2006). Three analyses were run with different covariates; neuropsychological tests which showed

highest effect size alone, qEEG parameters showing highest effect size alone and best neuropsychological test and qEEG parameters combined. Classification plots, including measures of sensitivity, specificity, and false positive and negative rates of the models and leave-one-out validated models were calculated. Receiver operator curves (ROC) was constructed and the area under the ROC curve (AUC) calculated and used to test differences in the models discriminative abilities.

Effect sizes were calculated using Microsoft Excel (Microsoft Corp.), AUC comparisons were done with MedCalc 14.4 (MedCalc software bvba), while other analyses were run with Predictive Analytics SoftWare (PASW) version 18 (SPSS Inc).

RESULTS

The groups show similar characteristics on the demographic variables with the age spread marginally shifted down in the TBI group. Among intelligence variables the TBI and control group differ significantly ($p < 0.01$) on all measure Demographic and intelligence data for the TBI and control group is presented in table 1.

Table 1: *Demographic and intelligence variables*

	TBI ($N = 20$)			Control ($N = 20$)		
	Cases (%)	Median (Mean)	IQR (SD)	Cases (%)	Median (Mean)	IQR (SD)
Sex						
Male	12 (60)			12 (60)		
Female	8 (40)			8 (40)		
Age (yrs)		32	18.5 – 41.75		32	19.75 – 43.75
Education (yrs)		12	11.25 – 15		12	12 – 15
Performance IQ		(108.89)*	(12.07)		(118.5)*	(9.34)
Verbal IQ		(110.42)*	(15.35)		(122.7)*	(9.65)
Total IQ		(110.47)*	(14.80)		(122.9)*	(8.39)

Note: IQR = Inter quartile range; SD = standard deviation; * = significant different mean between groups ($p < 0.01$).

Injury variables of the TBI group show a heterogeneous distribution of injury severity as described with the GCS score and duration of PTA. The most common cause of injury was traffic accidents (65%). 90% of the patients reported daily distress caused by their TBI at testing. Injury and outcome variables for are presented in table 2.

Table2: *Injury and outcome variables*

MOI	Cases (%)	GCS	Cases (%)	PTA	Cases (%)	GOSE	Cases (%)
Traffic Accident	13 (65)	13–15	8 (40)	<7 days	8 (40)	≤ 7	18 (90)
Fall	6 (30)	9–12	6 (30)	< 14 days	5 (25)	≥ 8	2 (10)
Other	1 (5)	3–8	6 (30)	> 14 days	7 (35)		

Note: MOI = mechanism of injury; GCS = Glasgow coma scale; PTA = Post-traumatic amnesia; GOSE = Glasgow outcome scale extended 3 months follow-up.

Neuropsychological tests

Within the neuropsychological test battery 7 of 24 tests showed a significant difference between the two groups after controlling for multiple comparisons. These seven tests were in the information processing speed and executive function domains only. These were TMT1 ($p < 0.001$, $d = 1.16$), TMT2 ($p < 0.001$, $d = 1.12$), and TMT3 ($p < 0.001$, ES = 1.17) and CWIT (reading) ($p< 0.012$, $d = 0.85$) for information processing speed. Verbal fluency (category) ($p < 0.0001$, $d = 1.47$), TMT4 ($p < 0.0001$, $d = 1.19$), and CWIT (inhibition/switching) ($p < 0.009$, $d = 0.88$). See table 3 for a full overview. Significant differences were found in reaction time ($p < 0.007$, $d = 0.91$) on the vCPT task and in the standard error of the reaction time ($p < 0.005$, $d = 0.95$). No significant differences were found in numbers of omissions and comissions. Results are presented in table 4.

Table 3: *Neuropsychological measures*

Test; mean (SD) or median (IQR: 25%-75%)	N	Patients	IS (<1.5 SD)	N	Controls	IS (<1.5 SD)	p-value	d_{pooled}	ES_{IQR}
Motor function									
Grooved Pegboard; dominant hand (sec)	20	67.35 (9.96)	2 (10)	20	64.95 (9.23)	1 (5)	0.434		
Grooved Pegboard; non-dominant hand (sec)	20	79.95 (15.73)	6 (30)	20	70.55 (8.09)	1 (5)	0.024		
TMT 5; motor speed	20	23.00 (16.25-32.00)	1 (5)	19	23.00 (18-28)	1 (5)	0.910		
Information processing speed									
TMT 1; visual scanning (sec)	20	25.85 (7.16)	4 (20)	20	19.20 (3.52)	0 (0)	0.001*	1.18	
TMT 2; numbers (sec)	20	35.80 (12.88)	3 (15)	20	24.30 (5.97)	0 (0)	0.001*	1.15	
TMT 3; letters (sec)	20	34.50 (29.25-41.75)	3 (15)	20	22.00 (19.50-27.50)	0 (0)	0.001*		1.17
CWIT; reading (sec)	20	24.5 (4.47)	2 (10)	20	21.5 (2.33)	0 (0)	0.011*	0.84	
CWIT; color naming (sec)	20	33.45 (8.29)	4 (20)	20	28.55 (4.25)	0 (0)	0.026		
Sustained attention									
CPT; hit RT (mill. sec)	18	392.25 (64.09)	2 (11.1)	20	388.23 (59.85)	1 (5)	0.843		
CPT; delectability	18	0.72 (0.48-0.91)	0 (0)	20	0.93 (0.60-1.30)	0 (0)	0.242		
CPT; hit RT by block	18	0.00 (-0.01-0.01)	1 (5.6)	20	0.00 (-0.0175-0.02)	0 (0)	0.976		
Visual Memory									
CMVT; hits	19	38.74 (1.91)	0 (0)	20	38.8 (2.30)	0 (0)	0.927		
CMVT; total correct	19	76.63 (4.47)	3 (15.8)	20	78.65 (6.47)	4 (20)	0.207		
CMVT; false	19	16.26 (4.31)	5 (26.3)	20	14.15 (5.80)	6 (30)	0.267		
CMVT; delayed	19	4.00 (3.00-6.00)	4 (21.1)	20	5.00 (4.25-6)	1 (5)	0.214		
Verbal memory									
CVLT; total recall trial 1-5	20	51.90 (10.61)	1 (5)	20	56.20 (6.83)	0 (0)	0.193		
CVLT; immediate recall	20	11.90 (2.82)	0 (0)	20	12.20 (1.94)	0 (0)	0.698		
CVLT; delayed recall	20	12.00 (3.24)	2 (10)	20	12.8 (2.19)	1 (5)	0.367		
Working memory									
Digit span backwards	20	6.9 (2.17)	--	20	7.9 (2.47)	--	0.182		
Letter-number sequencing	20	10.35 (2.52)	1 (5)	20	12.20 (2.95)	0 (0)	0.039		
Executive function									
Verbal fluency; category	20	39.15 (9.04)	2 (10)	20	54.25 (11.04)	0 (0)	0.0001*	1.50	
TMT 4; letter-number switching (sec)	20	82.30 (24.19)	1 (5)	20	57.80 (15.14)	0 (0)	0.0001*	1.21	
CWIT; inhibition (sec)	20	53.75 (12.39)	1 (5)	20	48.70 (7.08)	0 (0)	0.124		
CWIT; inhibition/switching (sec)	20	67.66 (18.92)	3 (15)	20	53.85 (10.76)	1 (5)	0.009*	0.90	

Note: *IS* = Impaired score; d_{pooled} = Cohen's *d* with pooled variance; ES_{IQR} = effect size with pooled IQR.
Patient and Controls columns show mean score with SD or median with IQR. Alpha levels are Bonferroni corrected within each category of tests (alpha = 0.05 / number of tests).

EEG measures

Two ERP measures were significantly different between the TBI and control groups after controlling for multiple comparisons. These were P3Go latency ($p < 0.002$, $d = 1.02$) and the P3NoGo amplitude ($p < 0.0003$, $d = 1.23$). Within the theta band variables significant differences were found after controlling for multiple comparisons at electrodes T3 ($p < 0.009$, $d = 0.96$) and Fp2 ($p < 0.01$, $d = 0.66$).

Table 4: vCPT results and q*EEG measures*

Test; mean (SD) or median (25%-75%)	n	Patients	n	Controls	p-value	d_{pooled}	ES_{IQR}
vCPT results							
Omissions	20	0.5 (0-1)	20	0 (0-1)	0.683		
Comissions	20	0 (0-1)	20	0 (0-1)	0.595		
Mean RT (ms)	20	415.5 (82.7)	20	355.15 (44)	0.007*	0.91	
Mean RT S.E. (ms)	20	10.65 (7.15-12.2)	20	6.85 (5.9-8.5)	0.005*		0.95
ERP measures							
P3a auditive amplitude (μV)	20	6.00 (4.50)	20	6.73 (4.17)	0.683		
P3a auditive latency (ms)	20	191.7 (28.41)	20	188.80 (13.46)	0.595		
P3Go amplitude(μV)	20	7.60 (2.47)	20	10.25 (2.62)	0.019		
P3Go latency (ms)	20	339.7 (30.56)	20	317.65 (26.35)	0.002*	1.04	
P3NoGo amplitude(μV)	20	9.27 (4.21)	20	13.67 (2.59)	0.0003*	1.26	
P3NoGo latency (ms)	20	371.8 (33.35)	20	364.6 (27.26)	0.459		
Theta band power							
Fp1(μV^2)	20	1.03 (0.67-2.25)	20	0.65 (0.37-1.18)	0.040		
Fp2(μV^2)	20	1.18 (0.69-2.50)	20	0.76 (0.47-0.90)	0.010*		0.66
F7(μV^2)	20	1.81 (1.07-2.75)	20	1.56 (0.88-2.20)	0.068		
F3(μV^2)	20	1.86 (0.94-2.33)	20	1.07 (0.92-1.39)	0.176		
F4(μV^2)	20	1.52 (1.03-2.28)	20	1.18 (0.81-2.35)	0.079		
F8(μV^2)	20	1.62 (1.03-2.33)	20	1.36 (0.81-2.35)	0.552		
T3(μV^2)	20	1.84 (1.24-3.10)	20	1.01 (0.74-1.82)	0.009*		0.96
C3(μV^2)	20	1.13 (0.67-1.57)	20	0.66 (0.50-1.00)	0.042		
C4(μV^2)	20	0.94 (0.59-1.69)	20	0.72 (0.49-1.05)	0.190		
T4(μV^2)	20	1.58 (1.03-2.23)	20	0.91 (0.76-1.54)	0.040		

Note: * = $p \leq (0.05/6) = p \leq 0.008$ for ERP measures and $p \leq (0.01)$ for theta band power

Sensitivity and specificity of measures in predicting group membership

Three logistic regression models were created using binary logistic regression. The model covariates were verbal fluency category, TMT4, and TMT1 for model 1; P3NoGo

amplitude, P3Go latency and T3 theta power for model 2.First run revealed non-significant Wald statistic indicating uncertain contributions to the models. TMT4 (Wald = 0.789, p = 0.375) and TMT1 (Wald = 1.745, p = 0.186) were removed from model 1 and P3Go latency (Wald = 3.130, p = 0.77) was removed from model 2. Model 3 had the covariates verbal fluency category, P3NoGo amplitude, and T3 theta power based on the results of models 1 and 2.

In these three final models omnibus test of model coefficients versus a model with intercept only was statistically significant$\chi^2(1, N = 40) = 18.903, p < .001$, $\chi^2(2, N = 40) = 21.532, p < .001$, and$\chi^2(3, N = 40) = 33.879, p < .001$ for models 1, 2, and 3 respectively. Hosmer and Lemeshow goodness of fit shows how well the model fits the data with p > 0.05 indicating good fit. Models 1, 2, and 3 did fit the data adequately with $\chi^2(6, N = 40) = 10.545, p= .103$, $\chi^2(8, N = 40) = 5.564, p= .696$, and $\chi^2(8, N = 40) = 6.167, p= .629$ for models 1, 2, and 3 respectively. Nagelkerke R^2 was $R^2 = .502$, $R^2 = .555$, and $R^2 = .762$ for models 1, 2, and 3 respectively. Logistic regression coefficients, Wald tests, and odds ratios for each of the three models are presented in table 5. Model classification, sensitivity, specificity, false positive rate and false negative rate in both immediate and validated models are presented in table 6.

Table 5: *Logistic regression of neuropsychological measures and qEEG parameters*

						95% CI for EXP(B)	
Variables	B	S.E.	Wald	Sig.	Exp(B)	Lower	Upper
Model 1							
Verbal Fluency Category	-.450	.138	10.645	.001	.713	.486	.835
Model 2							
P3 NoGo Amplitude	-.467	.171	7.421	.006	.627	.448	.877
Theta power T3	1.261	.550	5.251	.022	3.530	1.200	10.382
Model 3							
Verbal Fluency Category	-.523	.203	6.618	.010	.593	.398	.883
P3 NoGo Amplitude	-.377	.175	4.638	.031	.686	.487	.967
Theta power T3	1.513	.685	4.875	.027	4.542	1.185	17.408

Note: B = beta; S.E. = Standard Error; Exp(B) = Odds ratio; CI = confidence interval

As seen from table 6 neuropsychological tests (model 1) could predict correct group membership in 80% of the cases for both the TBI and control group. After validation these results were the same. EEG measures (model 2) had similar performance before validation while the validated model correctly classified 76% of the controls and 79% of the TBI patients. Neuropsychological and qEEG measures combined (model 3) correctly classified 95% of the controls and 90% of the TBI patients before validation and 85% of both groups after validation. Model 3 had the best performance both prior to and after validation. AUCs with confidence intervals are presented in table 7.

Table 6: *Classification table of logistic regressions models*

Observed	Predicted Control	Predicted TBI	Percentage Correct	Overall percentage	False positive rate	False negative rate
Model 1				80	20	20
Control	16	4	80			
TBI	4	16	80			
Model 2				80	20	20
Control	16	4	80			
TBI	4	16	80			
Model 3				93	5	10
Control	19	1	95			
TBI	2	18	90			
Model 1 (LOO validated)				80	20	20
Control	16	4	80			
TBI	4	16	80			
Model 2 (LOO validated)				78	21	24
Control	16	4	76			
TBI	5	15	79			
Model 3 (LOO validated)				85	15	15
Control	17	3	85			
TBI	3	17	85			

Note: LOO = Leave one out. All values are percentages.

Table 7: *Regression models AUC*

			95% CI for AUC	
Model	AUC.	S.E.	Lower	Upper
Model 1	0.864	0.0588	0.718	0.951
Model 2	0.880	0.0551	0.738	0.961
Model 3	0.955	0.0299	0.838	0.995
Model 1 (LOO validated)	0.840	0.0650	0.690	0.936
Model 2 (LOO validated)	0.827	0.0674	0.675	0.928
Model 3 (LOO validated)	0.910	0.0496	0.776	0.977

Note: AUC = Area under curve

There were no significant differences in AUC within the raw models. The same holds for the validated models, indicating small changes in model discriminative abilities with changed covariates. However, there were significant differences in AUC before and after validation ($z = 2.184$, $p = 0.0290$; $z = 2.448$, $p = 0.0144$; $z = 1.992$, $p = 0.0464$ for model 1, 2, and 3 respectively) indicating significant changes in model discriminative abilities after validation.

DISCUSSION

The patient population consisted of a heterogeneous mix both with regard to mechanism of injury, and injury severity measured with the Glasgow coma scale and duration of PTA. Overall the TBI patients had worse scores than the control group although on fewer tests than expected from reviewing the literature (Dikmen et al., 2009; Hannay et al., 2004, and Silver et al., 2009). After controlling for multiple comparisons, significant differences in group raw scores were found only in the domains of information processing speed and executive functioning. As several regions most vulnerable to TBI are involved in these functions (Gentry, 1994; Hartikainen, et al., 2010, and Hannay et al., 2004), this is not surprising. It was among tests measuring these functions that the largest effect sizes were obtained. The verbal fluency test showed a very large effect size of 1.50 and the trail making test also showed large effect sizes ranging in between 1.15 – 1.21. The color word

interference test also produced large effect sizes ranging from 0.84 – 0.90. Similar findings have been reported by (Skandsen et al., 2010; Dikmen et al., 2009, and Patry & Mateer, 2006). It was expected to find significant differences on measures of memory and sustained attention because previous research has shown at least some discrimination between TBI patients and controls on these measures (Strong & Donders, 2008; Gardner & Vrbancic, 1998; Loken et al., 1995, and Riccio et al., 2002). A possible explanation of this lack of positive findings could be the heterogeneity in the TBI group. Another reason might be the low sample size making it difficult to detect small group differences. Within the qEEG parameters included in this study it was expected to find lower amplitudes and longer latencies for the ERP components and a significant increase in theta power on the frequency specter magnitude variables. Significant group differences were found on the latency of the P3Go and the amplitude of the P3NoGo ERPs. Significant higher theta activity was observed at two electrodes, located in the frontal and temporal lobes. These findings are in line with previous research demonstrating increased latency and reduced amplitude (Roche et al., 2004; Larson et al., 2009; Potter & Barrett, 1999, and Lew et al., 2005) of ERPs and an increase in theta activity frontally and temporally (Duff, 2004; Thornton & Carmody, 2009) in response to TBI. The effect sizes of these group differences were large (d = > 1) for the ERPs and medium (ES = < 0.8) and large (ES = > 0.8) for the spectral measure in the temporal and frontal lobes respectively. Negative findings among the qEEG parameters also deserve some mention. It was expected to find a more consistent significant difference across electrodes with previous research demonstrating a wider distribution of increased theta activity following injury (Thornton & Carmody, 2009; Duff, 2004).

Effect sizes may give some information about the distance between the population means on the performance scale of a test. Generally in literature and in effect studies of psychological interventions there is cheer for relatively low effect sizes. The implications of

this will be that although the two groups have significant different performance on a test, there may still be a large overlap between the two groups' performances. Another important point is that significant differences alone will not give a good estimate of how big the difference actually is. With large groups even small differences will turn out significant and the opposite for small groups. To illustrate this; take the verbal fluency effect size of 1.5 in this study which is quite large. Still 30% of the groups distributions overlap, and the degree of overlap for the other tests are even larger.

Another way of looking at the tests' ability to discriminate between the two groups is to look at the subjects' standardized scores with respect to norms of each test. This was not possible for the qEEG parameters because no database with definite healthy controls was readily available. A SD of 1.5 below the norm data mean for each test was used as a cut-off point for impaired scores which allows a 5% rate of false positives. Uplifting maybe for the patients, or negative with regard to the tests' sensitivity to TBI, few patients had impaired scores < 1.5 SD. This indicates that the tests chosen in this study may have a low sensitivity to the effects of TBI. Since the testing was done only three months post injury and patients reported significant daily distress as a consequence of the injury (GOSE), one would expect the tests to indicate impaired scores in more patients. This is an important finding because in some cases patients not presenting with objectively measurable difficulties or deficits may be rejected by the health system. They may be referred to psychiatric care. While this could reduce some symptoms, it would not necessarily compensate for the causes. Many patients will be dependent on insurance payouts and social services (Dikmen et al., 2009). In order to be granted this money, insurance companies would rely more on objectively measures like the neuropsychological assessment than the patient's subjective experience (Bigler & Brooks, 2009). Hartikainen, et al., (2010) argue that the structured testing environment created to assess distinct functions may not be sensitive to the problems experienced in everyday

situations which affect patient total functioning and quality of life. It was on the measures with no significant differences most patients had impaired scores. Unfortunately this was also true for the normal control group and hence the non-significant results. This indicates that certain tests may show high sensitivity to TBI when testing patients, but in reality the test also has a low specificity in that healthy controls scores are also labeled as impaired. These findings are in line with previous research on TBI (Iverson, Brooks, & Holdnack, 2008, and Schretlen, Testa, Winicki, Pearlson, & Gordon, 2008) and calls for consideration of including other neuropsychological tests or inclusion of other measures that may contribute to a better "assessment-total" discrimination between patients and controls.

QEEG parameters were included in this study as an addition to the neuropsychological assessment and the TBI and control groups had significant different mean scores on several measures. The effect sizes obtained were large, but not as large as the best neuropsychological test. This could be interpreted to mean that the qEEG parameters included in this study are not worth including because they do not discriminate any better between the groups than the already included neuropsychological measures. That would be a premature conclusion given the possibility that adding qEEG might increase the sensitivity and specificity to the assessment and help make correct predictions about borderline cases. Binary logistic regression was applied to investigate this and the logistic regression analysis showed that the neuropsychological test (model 1) displaying the largest effect size could correctly classify 80% of both the TBI and control subject to their respective groups after validation. This demonstrates decent sensitivity and specificity. The same is observed for the qEEG parameters (model 2) before validation, however after validation the sensitivity to TBI drops by 5% to 75%. This is a lower performance than the neuropsychological test alone and may reflect the lower effect sizes of the qEEG measures. When combining test and qEEG measures (model 3) the model has a high sensitivity and specificity with correct classification

in 95% of the controls and 90% of the TBI patients. However, after validation these numbers drop respectively 10% and 5% to 85%. Still, this model has the best discriminative ability both before and after validation. These results supports the thought of qEEG measuring some important aspect of cognitive functioning which the neuropsychological test alone is not able to do. It seems that the neuropsychological test and the qEEG parameters correctly classify different individuals. They could potentially increase the non-overlap in group performance in the sense that borderline cases not correctly classified by only one of the measures alone may be correctly classified when they are combined.

Taking a closer look at the differences in discriminative ability as measured by the AUCs, it is apparent that the models perform decently (AUC > 0.826 after validation). There were no significant differences in the AUCs between the three regression models. Still, a 5% drop in the false negative and false positive rates is observed when adding the qEEG measures. The differences in the AUCs before and after validation were significantly different with the latter being more pessimistic. This demonstrates the tendency to overfit the regression model if not validated and stresses the importance of validation in predictive models.

The findings from the logistic regression analyses do not necessarily match the impression from the impaired scores discussed above with the results from the latter appearing more pessimistic. When comparing each subject's raw score to the normative score on the neuropsychological tests, the result appear to depend largely on properties of the norms being used. For example, a 60 year old TBI patient performing in normal range on the verbal fluency test is actually compared to the performance of people aged 60-69 years. There is reason to hypothesize that this patient might not have performed in the normal range if compared to persons aged 60 only. This could put confounding effects on assessment and bias inferences. However, high resolution norms for all tests may not be realistic. As pointed out

by Skandsen et al., (2010), in clinical practice a person's score must (today) be compared to normative data and when interpreting whether a score reflects true impairment or not this interpretation should be done with reference to intellectual capacity and the patient's performance on other cognitive tests. However, if the norm data used in all these measures have low sensitivity to the condition at hand, it will not matter how many tests one include in the assessment. By using classification with the logistic regression analysis the regression equation is calibrated to separate two known groups creating a "TBI signature" to match all subjects to. Perhaps in some cases an assessment using raw scores put into an analysis like binary logistic regression or classification by support vector machine would yield more sensitivity and specificity to the condition in question than using more general norms.

Limitations

First, TBI patients had significant lower verbal, performance and total IQ than normal controls. The normal controls displayed generally high intellectual abilities and may not represent the true variation in the normal population. This could contribute to some of the large effect sizes observed in this study. The control group was however, composed of individuals matching the TBI patients on both age and years of education and there is a possibility that some of these differences might demonstrate the adverse effects of TBI. Literature does report a reduced performance on intellectual abilities following TBI (Kersel et al., 2001).

The selection of control group members should be specified. All members of the control group were healthy individuals with no present or prior history of somatic or psychiatric illness. Using strict exclusion criteria one might reduce some of the normal variation in the population. However, if using a control group of assumed healthy individuals where several might have some condition affecting their test performance one can no longer

be certain that the effects being observed is due to the experimental group manipulation (TBI and not TBI).

Analyses were carried out on the whole group of patients creating room for error in not controlling for the effects of sex, age and other variables when conducting the statistical analyses. This was done because of the low sample size where further sub-grouping would heighten the risk of error, extreme score influence and departure from normality. The sample of this study do however to some extent match the characteristic of a TBI population in that we have more men than women, most are patients with a high GCS score, mechanism of injury and duration of PTA resembles that of a larger TBI population (Bruns & Hauser, 2003). This also counts in terms of generalizability. It is believed that the findings in this study may to some extent be generalizable to other TBI populations having the same characteristics.

In this study the binary logistic regression analyses were carried out on a small sample introducing several methodological challenges such as coefficient bias and difficulty validating the model. Classification with binary logistic regression is usually validated by using one part of the sample for training and the other part for testing. Because of the small sample size this was not possible in this study. However, leave-one-out (LOO) validation has been recommended by Bautista, Estanislao, Marti-Bonmati, & Paredes, (1999) and when applied to this sample it significantly adjusted the discriminatory abilities of the models, counteracting bias introduced by training and testing with the same subjects.

It can be argued that the validity of the analysis is reduced in that it utilizes only one neuropsychological measure. In clinical practice several tests are administered giving the clinician many variables to compare. However, in this study the best neuropsychological tests which have been documented to be sensitive to the effects of TBI were put up against the best qEEG parameters allowing a head-to-head comparison. Only one neuropsychological test

contributed significantly to the regression model. More neuropsychological tests and qEEG parameters might reach significance on the Wald statistic and contribute to a regression model with a larger sample.

The ERP approach may not be the most sensitive way to tap into the changes in neural activity after a TBI. By applying independent component analysis several subcomponents of the P300 complex could have been investigated. There is reason to believe that changes might be more evident in some components than others and therefore by using ICA one might achieve higher sensitivity and specificity. However, the grand average ERPs used in this study are well researched and specific deviances in these ERPs have been documented and replicated in this study.

CONCLUSIONS

As with other conditions that affect the everyday functioning of the patients and are potentially costly to society, assessment is important to ensure good patient treatment, rehabilitation and security. An important prerequisite for thorough assessments is high sensitivity and specificity of the assessment tools.

In this study neuropsychological tests measuring information processing speed and executive function were found to be sensitive to the effects of TBI. They produced significant difference in raw score means and showed large effect sizes. Compared to test norms, the number of patients showing scores in the impaired range was lower than expected and the number of control persons higher than expected in some variables. Thus, when using test norms, the sensitivity and specificity can be described as low, or at least not satisfying. Within the qEEG measures the P3NoGo amplitude, P3Go latency and temporal and frontal theta power turned out to be significantly different between the TBI and normal group and

displaying medium to large effect sizes, suggesting these measures as potential candidates in increasing TBI assessment sensitivity and specificity.

Application of binary logistic regression indicated an increased sensitivity and specificity in discriminating TBI patients from normal controls when including qEEG measures of P3NoGo amplitude and temporal lobe theta power. The contribution did not reach significance in means of AUC, but any reduction of false positive and negative rates are important. Although conclusions about definite increase in sensitivity and specificity of combined neuropsychological measures and qEEG parameters must be drawn with caution, this study indicates that qEEG may be a good candidate to measure something more than neuropsychological tests alone, and thereby increase the total assessment sensitivity and specificity in detecting effects of TBI.

Implications for further research and clinical practice

In order to further investigate the contribution of qEEG in TBI assessment more studies are needed, with more subjects allowing us to subgroup the sample and control for sex and age effects. In addition larger samples would yield higher statistical power and more reliable results.

Studies using independent component analysis of the P300 event-related potentials in TBI populations combined with neuropsychological measures have the potential to pinpoint differences in the component parts of the P300 complex and further link knowledge about injury effects, brain activity and cognitive performance. Studies involving repeated qEEG measurement and neuropsychological testing from the acute phase to some years after injury could give some information about progression and how qEEG measures relate to outcome. Also if there is some variability in the sensitivity and specificity of assessment at different times in the course of recovery.

Several neuropsychological tests showed low discriminative abilities on raw scores between a TBI and control group. This along with norms not fully optimal in detecting the subtle changes many patients report calls for debate on which measures are to be trusted, since these may have wide implications for patients and society costs.

QEEG is a potentially valuable addition to TBI assessment. QEEG is non-invasive and both time and cost effective compared to other possible assessment tools. In this study qEEG parameters displayed larger effect sizes than several neuropsychological tests and when combined with the neuropsychological tests showing the largest effect sizes, logistic regression results tended towards an increase in sensitivity and specificity. With this, qEEG parameters investigated in this study may be valuable assets in future TBI assessment to determine presence or absence of disability.

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