Chapter 8

Summary

Stroke and head injury are responsible for the majority of acute brain injury cases. While there has been considerable progress in the diagnosis and therapy of these conditions, further improvements are necessary. New parameters are needed to assess more accurately several aspects of the pathophysiology and consequences of acute brain injury. In this thesis, two diagnostic modalities are presented which are both aimed at improving several aspects of diagnosis and prognosis of acute brain injury.

The first part of this thesis reviews sequential stages of acute brain injury care. In the diagnostic phase, imaging studies are of great value, but also time consuming. The importance of an easily applicable diagnostic marker is underlined, which could also serve as a monitoring instrument during therapy and as an estimator of prognosis. In the post-acute phase, better quantification of cognitive deficits is desirable, to more precisely define outcome. S-100, a glial cell marker, and Neuron specific enolase and N-Acetyl-Aspartate, both neuronal markers, are introduced as biochemical serum markers of brain damage. The event related P300 potential is described as a tool for quantifying cognitive functioning in the post acute phase.

In Chapter 2, the temporal profile of a serum parameter of brain damage (S-100) after acute head injury, ischemic stroke and Transient Ischemic Attacks (TIA) is evaluated. Different temporal profiles are found for the three conditions. After head injury, early peak levels of S-100 are found, while after stroke peak levels occur after 3 to 4 days. In TIA patients, S-100 levels showed little variation over time. This is compatible with different pathophysiological mechanisms in stroke and head injury. In stroke, raised serum S-100 levels probably reflect peri-infarct reactive gliosis, while in head injury, direct injury to astrocytes and several other biochemical cascades may explain the early rise in S-100 levels. Raised serum S-100 levels reflected the degree of neurological deficit in both stroke and TBI patients, suggesting a role for S-100 as a co-predictor for outcome.

This finding is used in Chapter 3, where monitoring of stroke patients with biochemical serum markers is introduced during a phase 2 study with an AMPA antagonist in ischemic stroke patients. Patients who received the trial drug in the highest dose showed a significant transient worsening in their neurological status. This was accompanied by a higher than expected raise in serum S-100 levels, but not of serum NSE levels. These results are interpreted as possible evidence for glial cell toxicity in addition to neuronal dysfunction in the patients receiving the drug. Furthermore, it shows the possible use of biochemical serum markers to monitor experimental therapy.

In Chapter 4, biochemical serum markers are used for detection of reperfusion of the occluded vessel in acute ischemic stroke patients. It is demonstrated that serum levels of S-100 do not change rapidly in relation to reperfusion. However, reperfusion was associated with a transient rapid increase in serum NAA levels. It is suggested that enhanced neuronal production and release of NAA might be caused by the restoration of energy and serve to remove neuronal water that has accumulated during ischemia. This method of monitoring

reperfusion could provide an alternative for TCD monitoring of reperfusion, if the findings can be reproduced in a larger cohort of patients.

In Chapter 5, a new analysis method of the event related P300 potential is presented, and compared with conventional P300 analysis. While conventional P300 analysis relies on analysis of the 3 midline electrodes, source analysis uses topographical maps in combination with dipole source modelling. It is shown that with source analysis the temporally overlapping P3A and P3B components can be identified more often than with conventional analysis. The result is a considerable reduction in latency variability in control subjects. The possible consequences of this finding is that diagnostic test properties of P300 testing could in theory improve as a result of less overlap between the latency distributions of control subjects and patients.

In Chapter 6, the results of both P300 analysis methods are compared in a group of control subjects and a group of moderate to severe head injury patients. Based on the findings in Chapter 5, the hypothesis was that the latency distributions of controls and head injury patients would show less overlap using source analysis as compared to conventional analysis, permitting a better distinction between these groups. Using conventional analysis, mean P300 latency was delayed and P300 amplitude was reduced compared to controls, a finding which is often reported in the literature. However, quite contrary to our hypothesis, with source analysis, there was no difference in P3A or P3B latency between both groups. Instead, in 43% of patients, no P3A component could be identified, indicating reduced activity in brain areas involved in P3A generation. It is concluded that the often observed delay in mean P300 latency in head injury patients is a pseudodelay, caused by reduced amplitude of the P3A component, so that the P3B component with its normal later latency determines P300 latency in these patients. This result has important consequences for the neuropsychological interpretation of a delayed conventional P300 potential in head injury patients. Conventional P300 latency cannot be used to conclude that there was delayed early stimulus processing in head injury patients.

In Chapter 7, diagnostic properties of both P300 methods are compared in a group of head injury patients, using neuropsychological test results as the golden standard. Furthermore, MRI data were used to identify different pathofysiological subgroups of head injury patients. Source analysis P300 results correlated better with measures of divided attention and memory than conventional analysis results. Diagnostic properties were also better when using source analysis instead of conventional analysis. We found a non linear relation between contusional severity and P3A amplitude obtained with source analysis, with a trend towards mild head injury patients having lower P3A amplitudes when compared with patients with focal frontal and/or temporal injury on MRI. Further analysis of MRI results suggested that medial frontal damage was associated with low P3A amplitude, while orbitofrontal damage was associated with increased P3A amplitude. The finding of reduced ERP task performance in the mild head injury group suggested that motivational and other psychological factors may explain reduced P3A amplitudes in this group. Applying P300 testing to subgroups of patients with different

degrees of head injury severity based on imaging results may further facilitate the interpretation and diagnostic applicability of source analysis P300 results in patients with head injury.

In conclusion, both diagnostic modalities presented in this thesis provide further insight into pathofysiological phenomena during and after acute brain injury. For biochemical serum markers of brain injury, there is a role for monitoring and estimation of prognosis. For the P300 event related potentials there is a role in diagnosis and quantification of cognitive disorders after acute brain injury.