Evoked potentials in rehabilitation. A review

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Summary

Rehabilitation is a multidisciplinary field of growing interest. Evoked and event-related potentials could be useful prognostic, longitudinal monitoring and cortical remodeling tools. In spite of these many possible applications, the literature contains relatively few articles dealing with the use of these potentials in rehabilitation. This review outlines the main achievements that have, however, been recorded.

In relation to prognosis, there is general consensus among authors as regards the strongest indicators of poor and good outcome: respectively, the stable absence of somatosensory evoked potentials bilaterally in hypoxic-ischemic coma, and a return of mismatch negativity. Event-related potentials, which are related to cognition, are considered more suitable for prognostic purposes. In longitudinal monitoring, event-related potentials show that recovery processes are not linear and that they can even outlast functional recovery. Electrical correlates of language open up new fields for research in rehabilitation. Finally, several observations indicate that “training” of evoked and event-related potentials is possible, an approach that could increase the viability of cortical remodeling.

KEY WORDS: evoked potentials, rehabilitation, stroke, traumatic brain injury.

Introduction

Potentials arising in response to the application of external stimuli (auditory, visual, somatosensory) can be recorded from the human cortex. These potentials, called evoked potentials (EPs), are strictly linked to the external stimuli and arise after a short interval, due to their transmission along a line and to the cortical integration of incoming volleys. Another class of potentials is not linked to the physical quality of the stimuli, but rather to a cognitive process, involving attention, discrimination or task execution. These are called event-related potentials (ERPs). Both these classes of potentials have been thoroughly studied, with research focusing on:

– quantification of the dynamic physical activity of the underlying neuronal sources;
– modeling procedures, in efforts to identify spatiotemporal patterns able to explain much of the data variance;
– normative data in humans and the effects of gender, age and education;
– alteration of brain potentials in different types of disease.

As a consequence, the study of EPs has been confined to the sphere of mathematical investigation and to ancillary services in neurological departments. In spite of the high quality of many studies, electrophysiological techniques have been granted little space in the sphere of rehabilitation. Yet, recovery processes are of the utmost importance in the repair of acute brain lesions, as for example in the case of traumatic brain injury (TBI). As we will see, EPs and ERPs can provide prognostic clues in the rehabilitation field, and also be instruments of rehabilitation. This review looks at EPs and ERPs from a rehabilitative perspective; magnetic evoked fields and motor evoked potentials are not considered in detail.

Evoked potentials

Brainstem auditory evoked potentials (BAEPs)

There are few data on BAEPs. Serial monitoring of the central sensory pathway in TBI patients finds its main application not in the predicting of outcome but in the planning of the care of the patient for the preservation of neuronal function (1). Central somatosensory and auditory brainstem conduction times provide useful prognostic information in paralyzed or sedated patients, but when neurological examination is feasible the benefits of EP analysis are lost (2). BAEPs are reliable predictors of an unfavorable but not of a favorable outcome. However, EP results are more reliable than intracranial pressure, pupillary light reaction, and motor findings in predicting outcome (3). Moreover, in the rehabilitation field, the new era of otovestibular rehabilitation has arrived and BAEPs appear mandatory in this framework. Auditory symptoms play a minor role in so-called post-concussive syndrome, but they should nevertheless be considered and evaluated fully. Long-term auditory dysfunction (tinnitus, hyperacusis, hearing loss) following a blow to the head warrants both audiological tests and BAEPs (4,5). Serial BAEP recordings with simultaneous recordings of BAEPs and somatosensory EPs have been shown to provide good prognostic indices of a fa-
favorable outcome (6). BAEPs are applied to the monitoring of brainstem function in patients undergoing high-dose barbiturate therapy. The main limitations of EPs are the occurrence of peripheral acoustic damage, the electromagnetic sources of artifacts in the unit, and the possible administration of ototoxic drugs. Data on BAEP application in stroke are inconsistent. Only in supratentorial stroke have BAEPs been found to be significantly correlated with outcome after one month (7), but it should be borne in mind that outcome at one month cannot be considered definitive outcome. In conclusion, BAEPs can provide some information following a severe TBI in the acute stage. They can also be important in a later stage, when difficulties arise in daily life and rehabilitation is called for.

**Visual evoked potentials (VEPs)**

In the acute stage, VEPs are like BAEPs. They are reliable predictors of an unfavorable but not of a favorable outcome (3). However, although the importance of VEPs (in relation to potentials of other kinds) is of little relevance, they do have a bearing on rehabilitation when the effects of TBI are long lasting. For example, VEP amplitude is a function of cortical binocular integration, which is influenced by dysfunction of the ambient visual process. Base-in prism and bi-nasal occluders are an effective means of treating ambient vision disturbances resulting from head trauma, or post-trauma vision syndrome (8).

Abnormal VEPs are seen in one-third of head-injured patients (9). They are due to deranged synchronization of the activity of different brain regions (10). In post-stroke patients a relationship might exist between the left-right asymmetry of the scalp VEP and both the damaged-region-to-brain-area ratio and the functional outcome of rehabilitation. A modeling study showed that the left-right asymmetry is most likely the result of conductivity changes at the level of the damaged area, which, in turn, are probably associated with the patient’s functional status and evolution (11). Optometric rehabilitation deals with visual system deficits and recovery. Indeed, significant differences in visual system recovery were shown when comparing treated and untreated groups (12). VEPs may reveal abnormalities even in patients without vision complaints (13). In conclusion, VEPs are useful monitors in the diagnosis and rehabilitation of visual disturbances after TBI. Serial recording in multiple sclerosis is another interesting area that warrants further investigation.

**Somatosensory evoked potentials (SEPs)**

Of all the EPs, SEPs are the most extensively studied. Articles investigating SEPs fall into two major groups, namely: those considering the predictive value of SEPs in coma and those considering their predictive value in post-stroke rehabilitation. Studies of SEPs in comatose patients can be further divided into 2 subgroups on the basis of an optimistic application of SEPs to outcome (14-21). However, the scope for prognosis is actually very narrow. Adults in coma from hypoxic-ischemic encephalopathy with absent SEPs have <1% chance of awakening (19). Abolition of cortical SEPs and/or cortical middle latency auditory evoked potentials (MLAEPs) rules out the return to consciousness of post-anoxic comatose patients (100% specificity) (20). The bilateral absence of cortical evoked potentials, generated by thalamocortical tracts, reliably predicts unfavorable outcome in comatose patients after cardiac arrest, and correlates strongly with death or persistent vegetative state in severe brain trauma. Therefore, greater use of SEPs in anoxic-ischemic coma and severe brain trauma would identify those patients unlikely to recover and thus unlikely to benefit from costly medical care (18).

Meta-analysis surveys indicate that SEP results predict, with a high level of certainty, the likelihood of not awakening from a coma. No patient in whom somatosensory N20 and auditory potentials are absent regains consciousness. In post-anoxic patients, reduced cortical amplitude, too, is always associated with unfavorable outcome. The prognostic value of SEPs and MLAEPs in post-anoxic comatose patients depends on the cause of the coma. Measurement of response amplitudes is informative. In any case, the presence of short latency cortical somatosensory or auditory components is not a guarantee of a return to consciousness. Late components should thus be recorded (20).

Other authors have reached even more rigid conclusions (22-26). Asymmetric but also absent SEPs, both in acute and prolonged coma, can be found in patients with good outcome (22).

In severe TBI patients, EP abnormality reflected in long latency SEP patterns (as opposed to intermediate latency patterns) appears better able to reflect the extent and severity of brain dysfunction and overall clinical condition (23). Bilateral absence of SEPs is characteristic of a subgroup of adult non-traumatic comatose patients with a mortality rate of 100%. Conversely, the presence of SEPs is not necessarily an index of favorable prognosis (25).

Absence of cortical SEPs indicates a severe neuronal dysfunction, which may be completely reversible if the underlying disease does not lead to permanent structural damage (22,26). The usefulness of SEPs following stroke is still debated. Several authors recommend recording them because the presence or the absence of SEPs, following either upper or lower limb stimulation, can provide the clinician with some prognostic data (7,27-31). In all the subgroups (ischemic or hemorrhagic strokes, subarachnoid hemorrhage) investigated in one study (7), SEPs were found to correlate significantly with outcome at all three timepoints considered. BAEPs showed no correlation with outcome at first examination in infratentorial disease, nor at second examination in subarachnoid hemorrhage. In all other cases, BAEPs were correlated statistically significantly with outcome at all three timepoints (7). The recording of SEPs has been successfully used in children in order to obtain information about the functional status of central and cortical somatosensory pathways following major head injury (32,33). In Vietnam war veterans, a correlation was found between recovery from hemiparesis and subsequent normality of SEPs (34).

Neurophysiological measures alone are of limited value in predicting long-term outcome. However, predictive accuracy is substantially improved through the combined use of both SEPs and motor evoked potentials and clinical variables (35). But other authors stress the weak correlation between SEP amplitude exhibited and
Evoked potentials in rehabilitation

degree of limb motor impairment. The correlation between SEP amplitude and physical disability is not statistically significant. Contrary to prior reports, median nerve SEP appears to be weakly correlated with clinical measures of upper limb function in hemiparesis (36). An important area of investigation in the rehabilitation field is the enhancement of sensorimotor function by cutaneous electrical stimulation in non acute stroke. Cutaneous stimulation was delivered twice daily via a special glove/sock electrode (37). Modified Motor Assessment Scale, 10-meter walking test, paretic hand function, upper limb skin sensation and SEP normally classified as paretic upper limb and paretic lower limb improved significantly in the treated group after three weeks’ stimulation. When active hand treatment and placebo hand treatment were compared, a significant improvement in sensory and motor function was observed only in the treated group. Therefore, cutaneous stimulation had positive effects on motor performance, limb sensation and the configuration of SEP of the paretic limb in chronic stroke patients (37).

In conclusion, SEPs, being recordable in the presence of anesthetic or relaxant agents, may first be evaluated during the acute stage of coma treatment. Bilateral absence is associated with unfavorable outcome only in non traumatic coma. No real significance can be attached to the presence of SEPs: it is true that SEPs in stroke patients under rehabilitation show a weak correlation with outcome, but electrical stimulation can favor cortical remodeling.

Event-related potentials

N140

Beyond the limits of short-term intervals, cognitive potentials may provide answers to unsolved questions related to rehabilitation. In this regard, they have, compared to SEPs, been the subject of less debate. In one patient with right-hemisphere damage (38), SEPs for unilateral stimulation showed early components over contralateral somatosensory areas (P60 and N110) for both hands. Unlike control subjects, the patient’s P60 was smaller in amplitude for left-hand touch over the right hemisphere than for right-hand touch over the intact hemisphere. Bilateral trials with extinction revealed residual P60 and N110 components over the right hemisphere in response to the extinguished left touch. Thus, there is a residual unconscious somatosensory processing of extinguished touch. Tactile extinction can be caused by attenuation rather than elimination of somatosensory potentials in the damaged hemisphere.

As we saw earlier (37), cutaneous stimulation can be used as a remodeling tool. Other evidence exists. Forty patients were admitted to rehabilitation. Twenty were enrolled in a daily discrimination training task using an oddball paradigm with cutaneous electrical stimuli (39,40). The training period was three weeks. Twenty control patients were untrained. ERPs evoked by the stimuli were recorded from scalp electrodes during each training session. In the controls only two recordings were made, at baseline and after three weeks. During training, ERPs took the form of a giant positive-negative complex over the period 106-160 ms after the stimulus, followed by a smaller P300 component. The amplitude of the potentials was smaller over the affected hemisphere. In the treatment group N140 was present in three patients from the beginning and in 16 after three weeks’ training. Four of the untrained control patients showed N140 at baseline and only six after three weeks. In stroke patients, training facilitates the recovery of N140. The timing of the recovery of N140 is prognostic of general outcome since early recovery of this electrophysiological response is correlated with a higher functional independence measure (FIM) score on discharge (39,40).

P300

Long latency SEP patterns — unlike intermediate latency SEP patterns — have been found to correlate significantly with clinical disability as measured by the Disability Rating Scale (23). The passive P300 is useful in assessing the extent and severity of brain lesions (41). In non traumatic coma the presence of a P300 was significantly associated with awakening, but its absence did not preclude awakening. Thirty percent of the comatose patients had a P300 and a higher Glasgow Coma Score (GCS) (42). P300 can be useful in prognosis when stroke causes aphasia. A passive P300 auditory ERP paradigm was applied every month for 6 months to seventeen right-handed patients suffering from global aphasia caused by a recent stroke. Twenty age-matched healthy volunteers were the controls. Aachen subtests were used for evaluating comprehension. Only a minority of the patients displayed the P300 at baseline, and these patients had the best outcome on the Aachen comprehension subtest. The latency of P300 was longer than in controls. Latency and amplitude changed over time in an unpredictable manner. The number of patients presenting the P300 also fluctuated, since it was found, from month to month, that some patients might regain, and others lose, the potential. Therefore, passive P300 is a monitor of recovery following global aphasia. A single passive P300 recording is useful for prognostic purposes. Repairing mechanisms in the first 6 months show a non linear trend. Nevertheless, electrophysiological techniques are a useful, non invasive and inexpensive means of following cortical events over time on a millisecond-to-millisecond basis, and they provide information about repair mechanisms in the nervous system (43).

The hypothesis, based on several previous reports, of cortical non responsivity of patients with akinetic mutism, was not supported by ERP examination. Electrophysiological investigation can collect information about the mental state of these patients, provided the stimuli and tasks possess a wide range of informational complexity and motivational value (44). Passive P300 was recorded in 9 out of 17 patients who were in vegetative state. In this case, the rare stimuli used were the patients’ names — thus, stimuli that tapped on their emotions (45). P300 has been widely applied to TBI survivors (46-54). Evidence suggests that despite excellent behavioral recovery, subtle information processing deficits involving attention may nevertheless persist long after the original injury and may not be apparent on a variety of standard psychometric measures. Visual
sensory processing may be spared, but higher-order visual processing involved in stimulus classification may be compromised (52). The shift and maintenance of attention can be impaired. The presence of numbing with reduced attention processing (P300) is consistent with a relationship between disordered arousal and attention in post-traumatic stress disorder, in the context of which an impaired allocation of attentional resources to the processing of deviant stimuli can be observed. P300 may well be useful in predicting difficulties with activities of daily living in patients with Parkinson’s disease (55). Implications of delayed onset have been discussed in relation to P300 applications in the clinical assessment of dementia and aging-associated cognitive alterations (56).

Brain infarction delays the P300 and temporarily distorts its age-related physiology. The increase of the P300 latency seems to be associated with post-stroke depression in minor ischemic stroke (57). Virtual reality may prove useful for training individuals to use a brain-computer interface (BCI). It could provide complex and controllable experimental environments during BCI research and development as well as increase user motivation. One study (58) demonstrated the robustness of the evoked potential P300 component in virtual and non virtual environments.

Mismatch negativity (MMN)

This ERP is an index of the integrity of cerebral processes that respond automatically to deviations from regularity in the acoustic environment. Results of MMN testing in different patient groups are central to the interpretation of an assumed abnormality of processing or storing of acoustic features (59). Highly significant correlations exist between long-latency ERP components and 3-month outcome. Short-latency EPs, brainstem (wave I-V) and somatosensory conduction times also significantly correlate with TBI outcome. Pupillary response patterns, APACHE II and GCS correlate significantly with outcome, as do the retrospective measures of duration of coma and post-traumatic amnesia in survivors. However, due to variance of long-latency potentials, absolute values cannot be relied upon for prognosis, even in controls. The presence of MMN predicted the return of consciousness (89.7% sensitivity and 100% specificity) and significantly correlated with 3-month outcome. The MMN elicited by deviance occurring to the left of the patients was reduced compared with that elicited by deviance occurring to the right (61).

P340

When a same word is delivered to the subject, a positive component at 340 ms is recorded following the N100-P200 complex. This potential is automatic, phonologically driven, independent of habituation, specific for verbal material, and significantly lateralized to the left side in right-handers. The left-handed group is less homogeneous. In a study group of ours, seven out of 18 subjects (38.8%) had a right lateralization, whereas in 5 subjects (27.7%) the positive potential was shifted to the left side. Inter-hemispheric differences were significant. Finally, 6 subjects (33.3%) had a bilateral representation. The results indicate the usefulness of ERPs in the study of language processing. Spoken words appear to be a very appropriate tool, because they permit the study of electro-encephalographic changes on a millisecond-to-millisecond basis. In the Italian language, at least, they offer a safe, inexpensive and reliable means of identifying hemispheric location of language (62). Two patients suffering from Broca’s aphasia lacked a P340, even after one year (63).

N400

Although median nerve SEP continues to be a reliable predictor of unfavorable outcome in severe TBI, the implementation of speech-evoked ERPs may be helpful in predicting favorable outcomes. The strength of the latter test seems to compensate for the weakness of the former (53).

Language function in stroke patients can be evaluated, independently of behavior, using electrophysiological measures that correlate strongly with traditional neuropsychological test scores (64). Electrophysiological measures link ERPs with neuropsychological data to an unprecedented degree. Given this high correlation, a regression line could reasonably be used to estimate a patient’s language ability solely on the basis of ERPs (65). The success of this approach has demonstrated that ERPs can be used to evaluate reliably an individual’s reading and speech comprehension abilities, independently of his/her behavioral and speech production impediments. In contrast to traditional neuropsychological assessment, these ERP methods can discern the cognitive strategies used by an individual to perform a task (66).

Electrophysiological techniques have been applied to syntactic on-line processing during auditory sentence comprehension in patients with Broca’s aphasia (67). The sentences were either syntactically correct or contained violations of subject-verb agreement. The healthy subjects and the non aphasic patients with a right-hemisphere lesion showed essentially the same pattern, i.e., a P600 effect as response to the agreement violations. The overall group of Broca patients did not show this sensitivity. The largest deviation from the standard P600 effect indicated the most severe syntactic comprehension impairment. My group has found that during listening to words in an oddball paradigm a large negative wave is produced peaking at about 400 ms. The wave duration is proportional to the cognitive load, being larger in the case of non words and smaller in the case of high-frequency words, i.e., words frequently encountered in daily communication. These potentials are very sensitive to cognitive decline (63,68). They are likely to find extensive application in the field of early-onset Alzheimer’s disease (68,69).

Contingent negative variation (CNV)

In healthy subjects both the early, frontal-maximum, and the later vertex-maximum, components of the CNV have been found to be larger on GO than NO-GO trials. In patients, the early frontal CNV wave did not distinguish between GO and NO-GO trials, and the late CNV was less able to distinguish between these trial types than the late CNV of the control group. These CNV abnormalities may reflect impairments in selective orienta-
Evoked potentials in rehabilitation

Concluding remarks

The enthusiasm with which SEPs were initially applied waned following the emergence of a decline in their predictive value: TBI patients apparently showing a bad outcome nevertheless survived, and the reverse was also seen to occur. Moreover, the application of EPs presents several limitations, namely: i) drugs influence recording; ii) potentials are not always available; iii) presence is a good prognostic indicator, but absence does not signify unfavorable outcome; iv) many variables are correlated with the outcome but the relationship is not a strong basis for prediction of a good quality of life. As regards prognosis in the acute stages, we can draw the following conclusions: i) the best indicator of bad outcome is stable absence of SEPs bilaterally in hypoxic-ischemic coma; ii) the best indicator of good outcome is a return of MMN; iii) ERPs are more suited to prognosis, since they are related to cognition. Magnetic evoked potentials and motor evoked potentials open up new scenarios and may offer a further contribution (73). However, magnetic field recordings are costly and their availability in emergency situations is nil. Transcranial magnetic stimulation (TMS) has been used in several ways to identify short- and long-term patterns of cortical remodeling during motor recovery. Paired TMS in a paired-pulse paradigm is now regarded as a gold standard in the testing of cortical inhibitory and excitatory intracortical circuits. Motor response evoked by a suprathreshold test magnetic stimulus is depressed by a previous subthreshold conditioning pulse with short interstimulus interval. The depression is supposed to reflect the activation of GABAergic interneurons and therefore intracortical inhibition on the corticospinal neurons. On the other hand, the facilitation seen at longer intervals reflects the activation of glutamatergic interneurons, which has excitatory effects on the cortical output. Therefore, cortical outputs can be studied through paired stimulation modulation. TMS has been considered to activate the corticospinal neurons transsynaptically at cortical level (74). However, there is still uncertainty as to whether potential amplitude only reflects corticomotoneuron excitability, regardless of any modulation at spinal level. Neuroimaging provides useful information when key cognitive processes occur but cannot detect short-lived events lasting milliseconds, and, unlike electrical stimulation, it has yet to become routinely used as a tool in rehabilitative practice. Nevertheless, the amount of information provided by neuroimaging in the field of neuroplasticity is impressive. In view of their limitations, their variability in normal individuals, and their limited standardization and validation, it is only with caution that we can regard EPs as prognostic indices. That said, ERPs might be applied as a useful supplement to neuropsychological assessment methods (75). It is to be hoped that, in the future, electrophysiological laboratories will produce fewer episodic evaluations and will, instead, seek to forge stronger links with the field of rehabilitation. This will lead to increased availability of time-series studies and a better understanding of both spontaneous mechanisms of repair and cortical remodeling induced by external manipulations, both of which are the targets of rehabilitative practice. Nevertheless, the amount of information provided by neuroimaging in the field of neuroplasticity is impressive.

Table I - Main statements of interest in rehabilitation.

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intervention. Table I summarizes the achievements in the field produced by such an overlapping of electrophysiology and rehabilitation.

References

