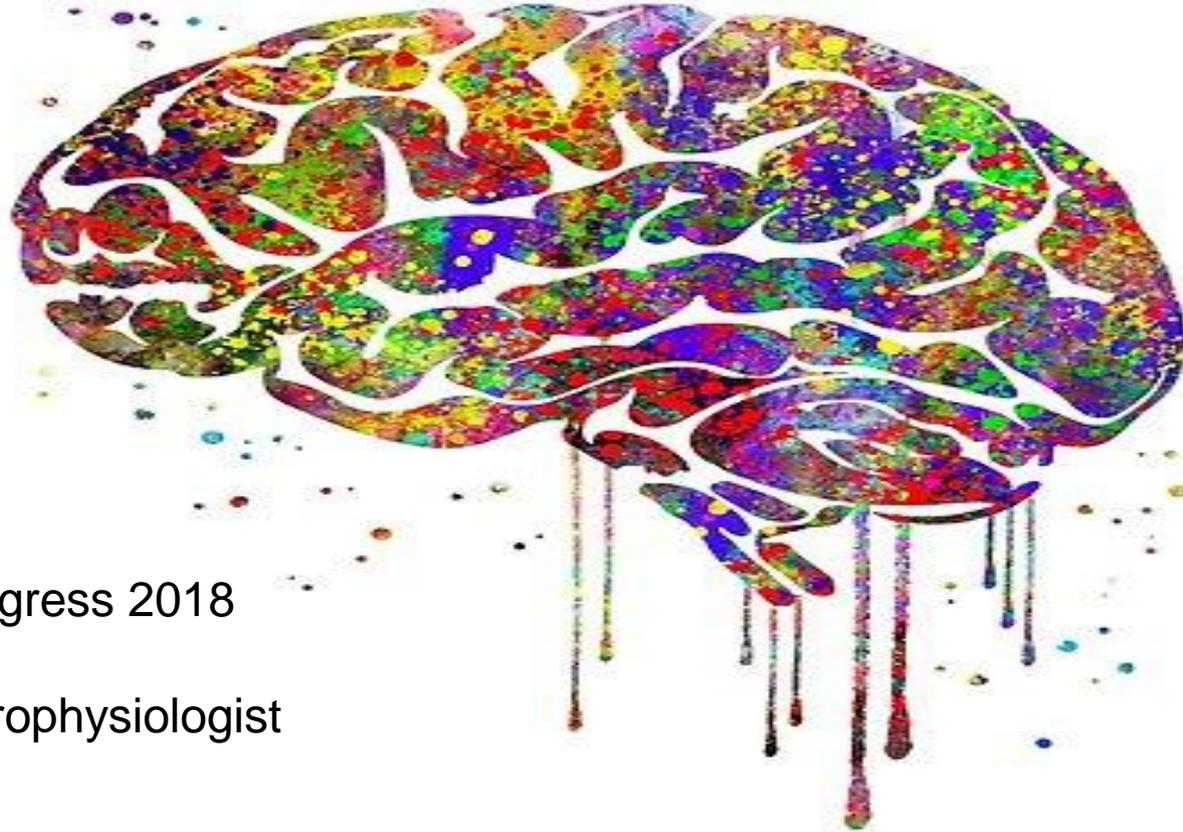
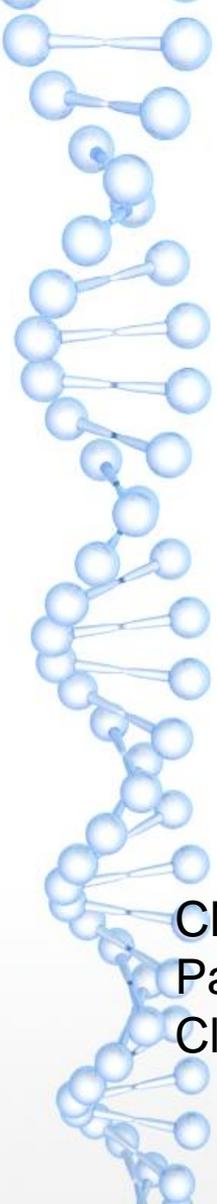


Frontiers of Coma Prognosis



CNSSA Congress 2018
Paul Blom
Clinical Neurophysiologist

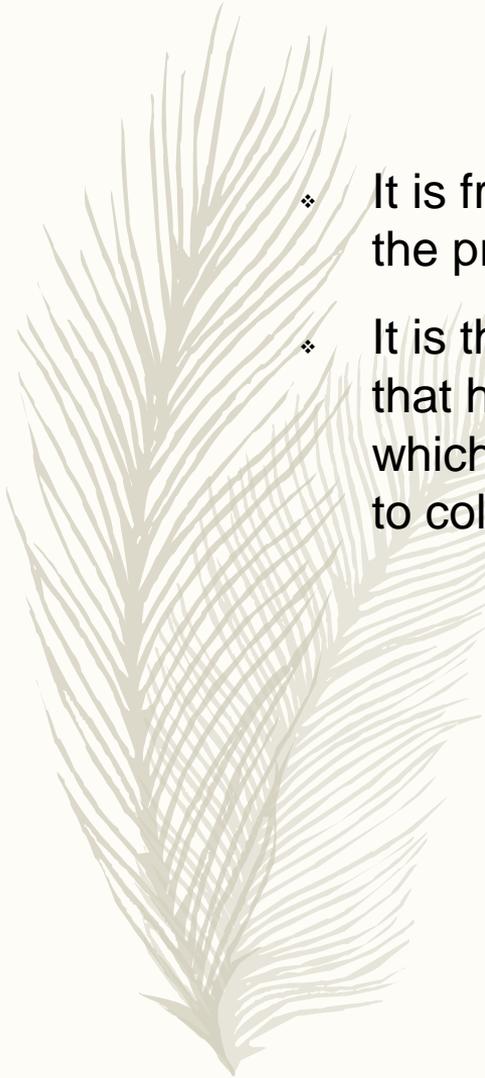


Introduction

- ❖ The assessment of patients in coma is a medical emergency.
- ❖ The cause should be identified and, where possible, corrected and the brain provided with appropriate protection to reduce further damage.
- ❖ It then becomes important to identify those patients for whom the prognosis is hopeless and in whom the institution or persistence of resuscitative measures is inappropriate, serving only to prolong the anguish of relatives and carers.

Introduction

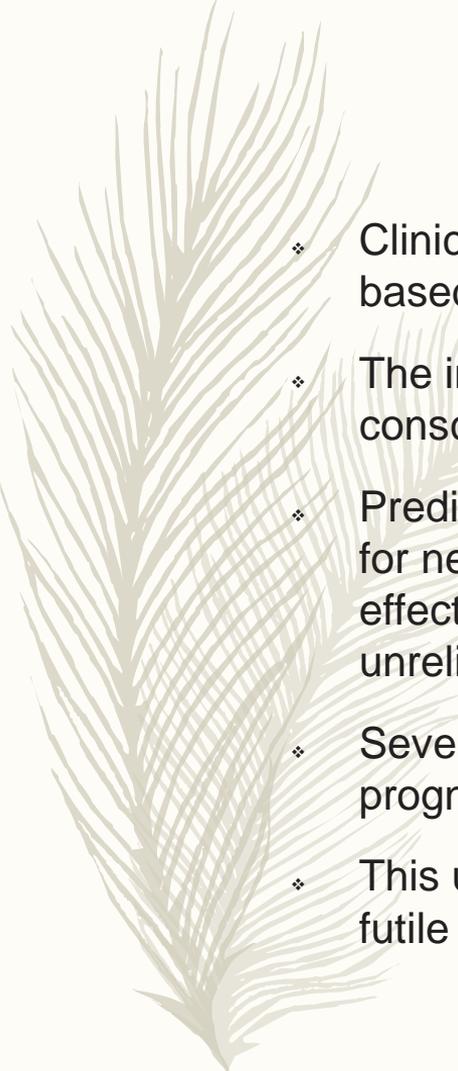
- ❖ It is frequently the neurologist to whom the physicians turn, to establish the prognosis of the individual in coma.
- ❖ It is therefore important that the neurologist has a full supportive team so that he or she can reasonably and accurately determine those factors which help in identifying prognosis and thereby provide reasonable advice to colleagues and the relatives and friends of the patient.



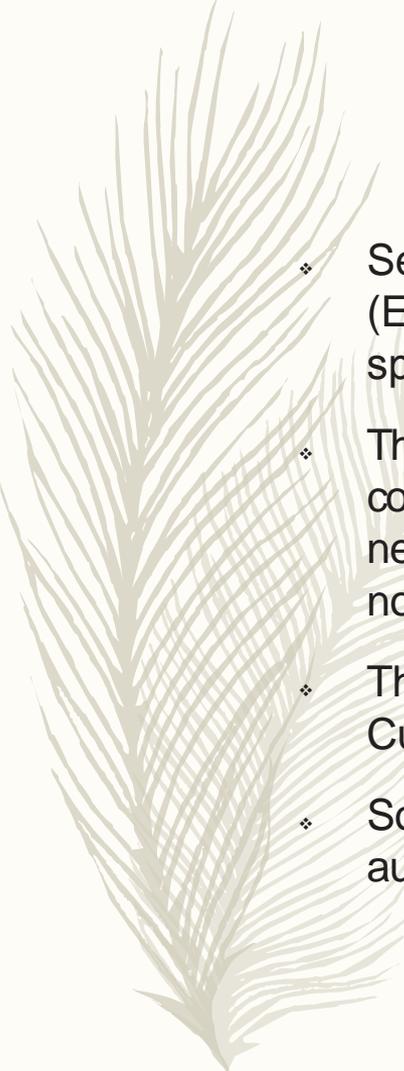
Introduction

- 
- ❖ Knowledge of the anatomical basis of coma is essential for competent evaluation but must be combined with an understanding of the many, often multi-factorial, medical conditions that result in impaired consciousness.
 - ❖ Consciousness is a state of awareness of self and the environment.
 - ❖ This state is determined by two separate functions: awareness (content of consciousness) and arousal (level of consciousness)
 - ❖ These are dependant upon separate physiological and anatomical systems. Coma is caused by disordered arousal rather than impairment of the content of consciousness, this being the sum of cognitive and affective mental function, dependent on an intact cerebral cortex.
 - ❖ The absence of all content of consciousness is the basis for the vegetative state.

Introduction

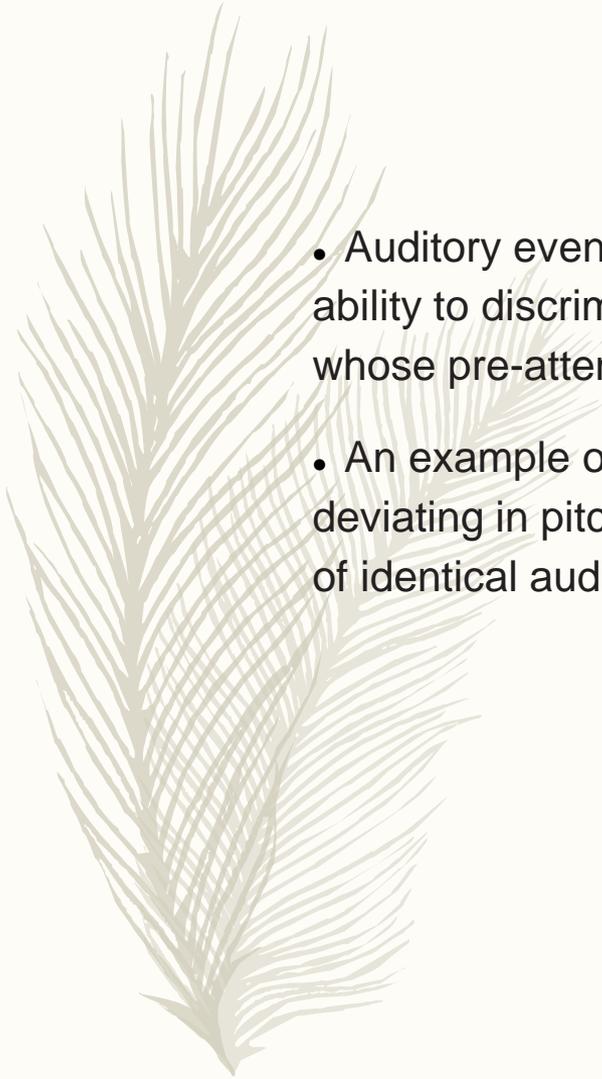
- 
- ❖ Clinicians must establish realistic goals for the management of comatose patients based on the potential for functional recovery.
 - ❖ The initial concern is uncertainty about whether or not the patients will recover consciousness.
 - ❖ Predicting the recovery of consciousness is complicated by the use of hypothermia for neuroprotection, the presence of metabolic derangements, and the prolonged effect of anaesthetic and sedative agents, which make the clinical examination unreliable, even after normalization of body temperature.
 - ❖ Several imaging diagnostic tests can be used, but their accuracy for estimating prognosis based on the magnitude and extent of the brain damage is also limited.
 - ❖ This uncertainty may lead to premature withdrawal of care in some patients or the futile continuation of life support in others.

Introduction

- 
- ❖ Sensory-evoked potentials are voltage fluctuations within the electroencephalogram (EEG) associated with a series of sensory events elicited by the presentation of specific sensory stimuli within the somesthetic, visual, or auditory domains.
 - ❖ These potentials may provide a reliable assessment of the functional status of the brain during coma. The absence of the early somatosensory-evoked potentials and particularly the negative wave called *N20* in comatose patients is a good indicator of the likelihood of non awakening
 - ❖ Their presence, however, does not guarantee the recovery of consciousness. Currently, no practical tool that accurately predicts awakening is available.
 - ❖ Some studies have suggested that patients who show higher-order cortical processing of auditory stimuli during the course of coma may be more likely to make a good recovery.

Introduction

- Auditory event-related potentials (ERPs) in particular, which assess the subject's ability to discriminate different acoustic stimuli, can identify those comatose patients whose pre-attentive auditory memory remains active.
- An example of this is the odd-ball paradigm where an occasional acoustic stimulus deviating in pitch, intensity, duration, or a combination of these is interspersed in a train of identical auditory stimuli.



Introduction

- ❖ The most distinctive response to this paradigm is a negative wave called *mis match negativity(MMN)*, which has been identified as a good indicator for the recovery of consciousness in comatose patients.
- ❖ Despite its potential use, this technique has not been implemented in clinical practice. In a study done by Rodriguez et al published in the Journal of Critical Care in 2016 - which will be discussed throughout the presentation - they assessed the value of MMN and other auditory-evoked potentials (AEPs) including middle-latency and brainstem potentials for predicting recovery of consciousness.

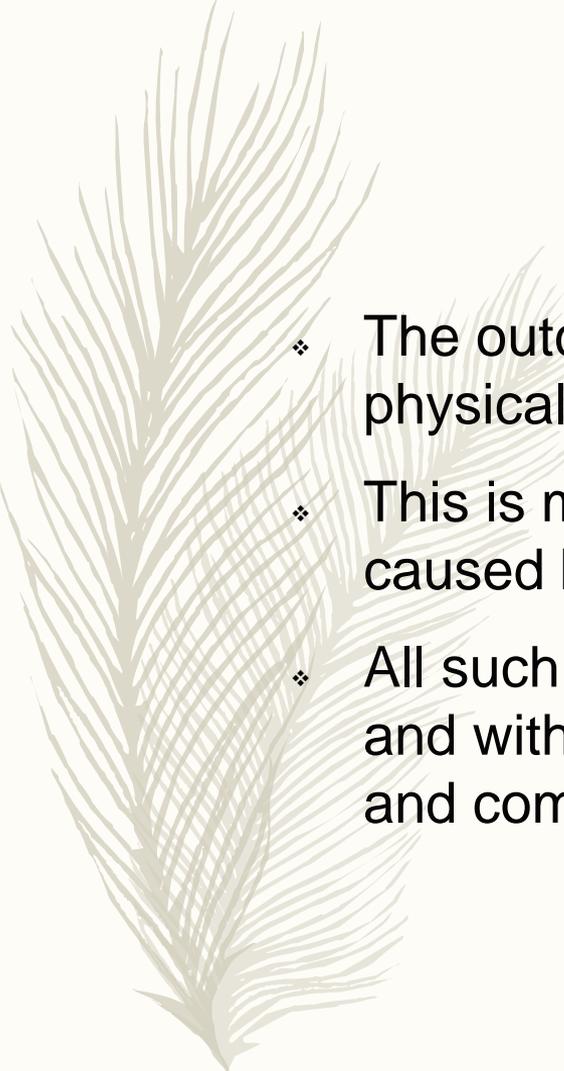
HONEY, I'VE DECIDED
TO SELL YOUR
CORVETTE.



©2014, KIM McPHERSON/DIST. BY UNIVERSAL UCLICK

Five months into his coma, Brad's wife finally finds the words to bring him back to life.

Aetiology

- 
- ❖ The outcome of coma is related to the cause independent of the physical signs, depth of coma or length of coma.
 - ❖ This is most important and shown most dramatically in coma caused by drug overdose.
 - ❖ All such patients should be regarded as potentially salvageable and with a good prognosis provided that they can be supported and complications are avoided during the period of coma.

Aetiology

- 
- ❖ Patients with drug overdose coma frequently appear deeply comatose with depressed brain stem reflexes because of the effects of the drugs upon the brain stem, yet may show disproportionately high levels of motor activity.
 - ❖ In general, metabolic causes of coma have a better prognosis than anoxic–ischaemic causes.
 - ❖ Cerebrovascular disease (subarachnoid haemorrhage or stroke) carries the worst prognosis of all.

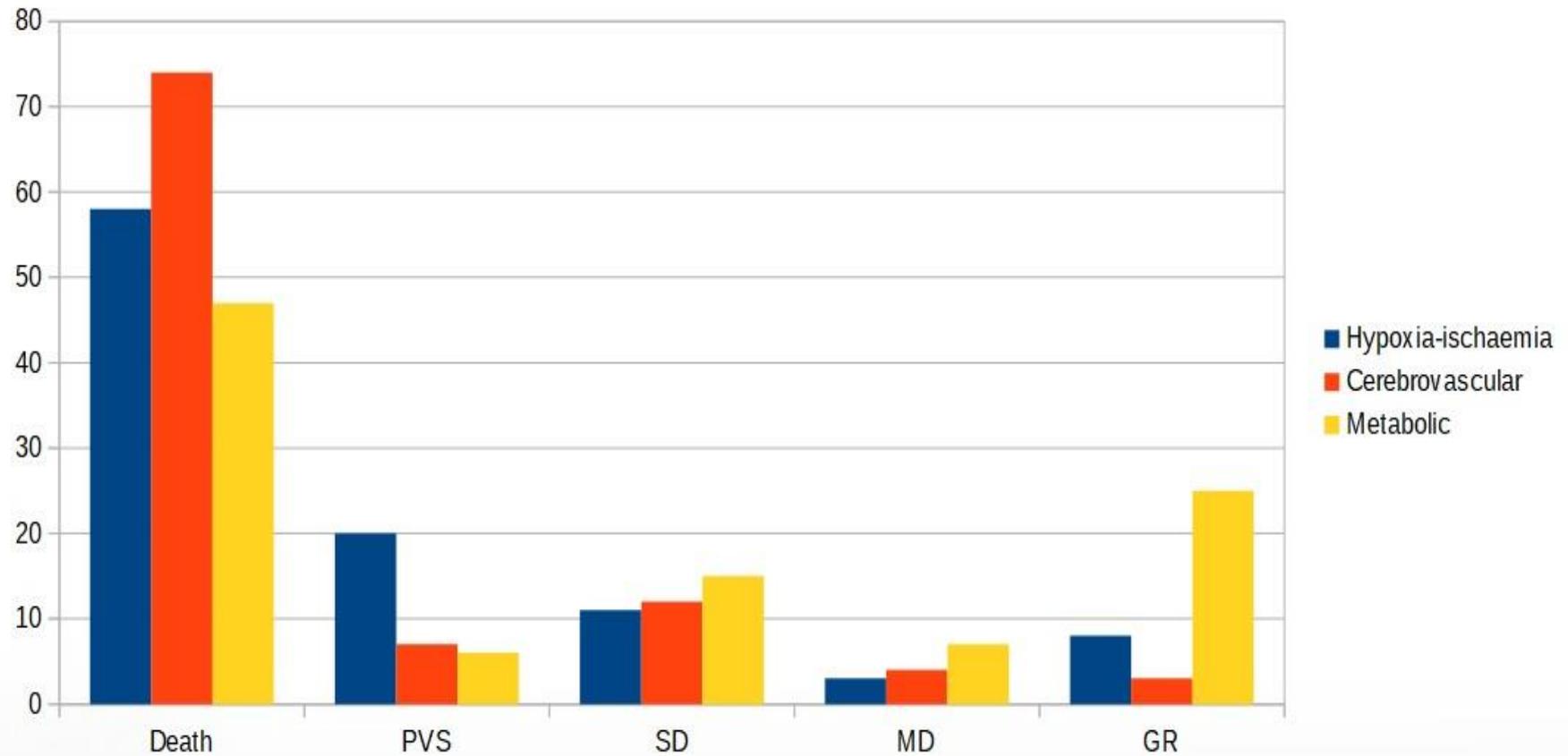
Aetiology

Table 1 Aetiology as a prognostic factor

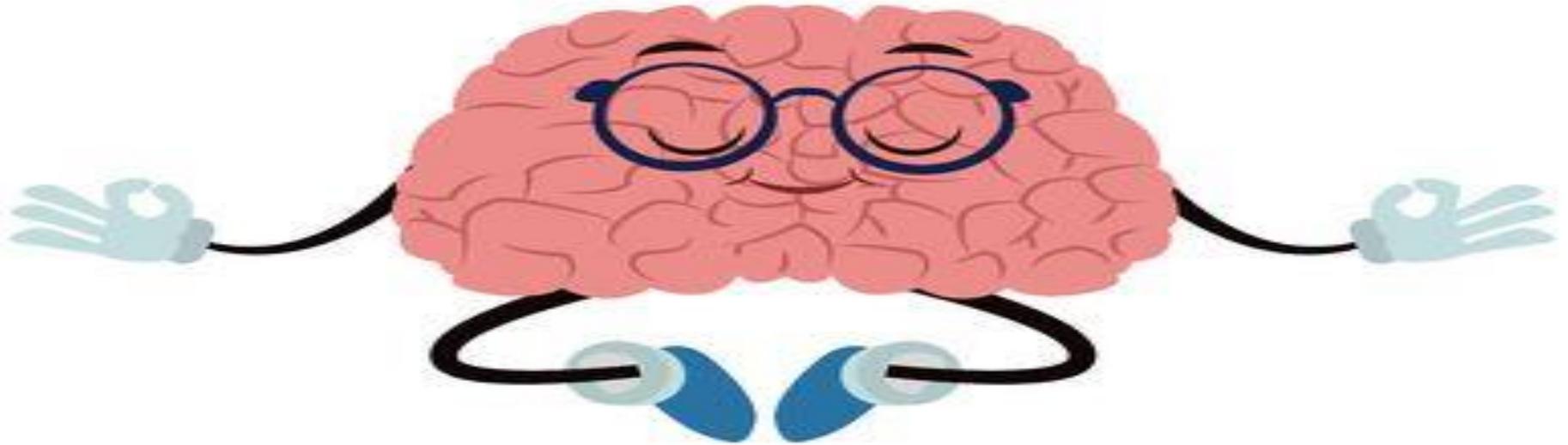
| | Outcome (%) | | | | |
|-------------------|-------------|-----|----|----|----|
| | D | PVS | SD | MD | GR |
| Hypoxia-ischaemia | 58 | 20 | 11 | 3 | 8 |
| Cerebrovascular | 74 | 7 | 12 | 4 | 3 |
| Metabolic | 47 | 6 | 15 | 7 | 25 |
| Total | 61 | 12 | 12 | 5 | 10 |

D, death; PVS, persistent vegetative state; SD, severe disability; MD, moderate disability; GR, good recovery.

Aetiology



Resting-State Electroencephalography in Disorders of Consciousness



Resting-State Electroencephalography in Disorders of Consciousness

- ❖ Neuro-imaging technologies have been developed as important methods for assessing the brain condition of patients with disorders of consciousness (DOC).
- ❖ Among these technologies, resting-state electroencephalography (EEG) recording and analysis has been widely applied by clinicians due to its relatively low cost and convenience.
- ❖ EEG reflects the electrical activity of the underlying neurons, and it contains information regarding neuronal population oscillations, the information flow pathway and neural activity networks.

Resting-State Electroencephalography in Disorders of Consciousness

The EEG Analysis for Diagnosis:

- ❖ Since minimally conscious state (MCS) patients are considered to benefit relatively easily from some specific treatments, compared to vegetative state (VS), the ability to differentiate an MCS from a VS would offer great value in making decisions about treatment.
- ❖ In clinical practice, many standardized behavioural scales are used in the assessment of consciousness of brain-injured patients, such as the Glasgow Coma Scale (GCS).
- ❖ The GCS is widely used in the early hours of a patient's admission, and used throughout the recovery.

Glasgow Coma Scale



| Glasgow Coma Scale | | |
|-----------------------------|---|----------|
| Response | Scale | Score |
| Eye Opening Response | Eyes open spontaneously | 4 Points |
| | Eyes open to verbal command, speech, or shout | 3 Points |
| | Eyes open to pain (not applied to face) | 2 Points |
| | No eye opening | 1 Point |
| Verbal Response | Oriented | 5 Points |
| | Confused conversation, but able to answer questions | 4 Points |
| | Inappropriate responses, words discernible | 3 Points |
| | Incomprehensible sounds or speech | 2 Points |
| | No verbal response | 1 Point |
| Motor Response | Obeys commands for movement | 6 Points |
| | Purposeful movement to painful stimulus | 5 Points |
| | Withdraws from pain | 4 Points |
| | Abnormal (spastic) flexion, decorticate posture | 3 Points |
| | Extensor (rigid) response, decerebrate posture | 2 Points |
| | No motor response | 1 Point |

Minor Brain Injury = 13-15 points; **Moderate Brain Injury** = 9-12 points; **Severe Brain Injury** = 3-8 points

Resting-State Electroencephalography in Disorders of Consciousness

The EEG Analysis for Diagnosis:

- ❖ However, a high ratio of misdiagnoses can be caused by clinicians' subjective judgements, motor function injuries, and patients' fluctuating levels of awareness.
- ❖ Spectrum powers have demonstrated the ability to discriminate between MCS and VS. VS patients have shown increased delta activity but decreased alpha activity, compared to those with MCS.
- ❖ In comparison with healthy subjects, VS patients have shown higher delta and theta frequencies, and both MCS and VS patients have shown decreased alpha activity.

Resting-State Electroencephalography in Disorders of Consciousness

The EEG Analysis for Diagnosis:

- Along with the diffuse slowing commonly observed in DOC patients, several additional patterns have been reported.
- In case of supra-tentorial lesions, polymorphic focal delta rhythm can be visible over the damaged regions.
- If there is asymmetric brain damage, the EEG will likely also be asymmetric; the electro-genesis of one hemisphere can appear almost normal whereas that of the other is severely impaired.
- Still a precise location of a lesion cannot be achieved with the EEG as its spatial resolution is low.

Resting-State Electroencephalography in Disorders of Consciousness

The EEG Analysis for Diagnosis:

- ❖ When the lesions are infra-tentorial, the EEG can display a close to normal activity as it is sometimes but not always the case in locked in patients (LIS).
- ❖ Another pattern found in DOC patients is burst suppression.
- ❖ When the entire recording is flat or isoelectric, i.e. there is no cerebral activity of more than two micro volts; the patient can be in a state of electrocerebral inactivity.

Resting-State Electroencephalography in Disorders of Consciousness

The EEG Analysis for Diagnosis:

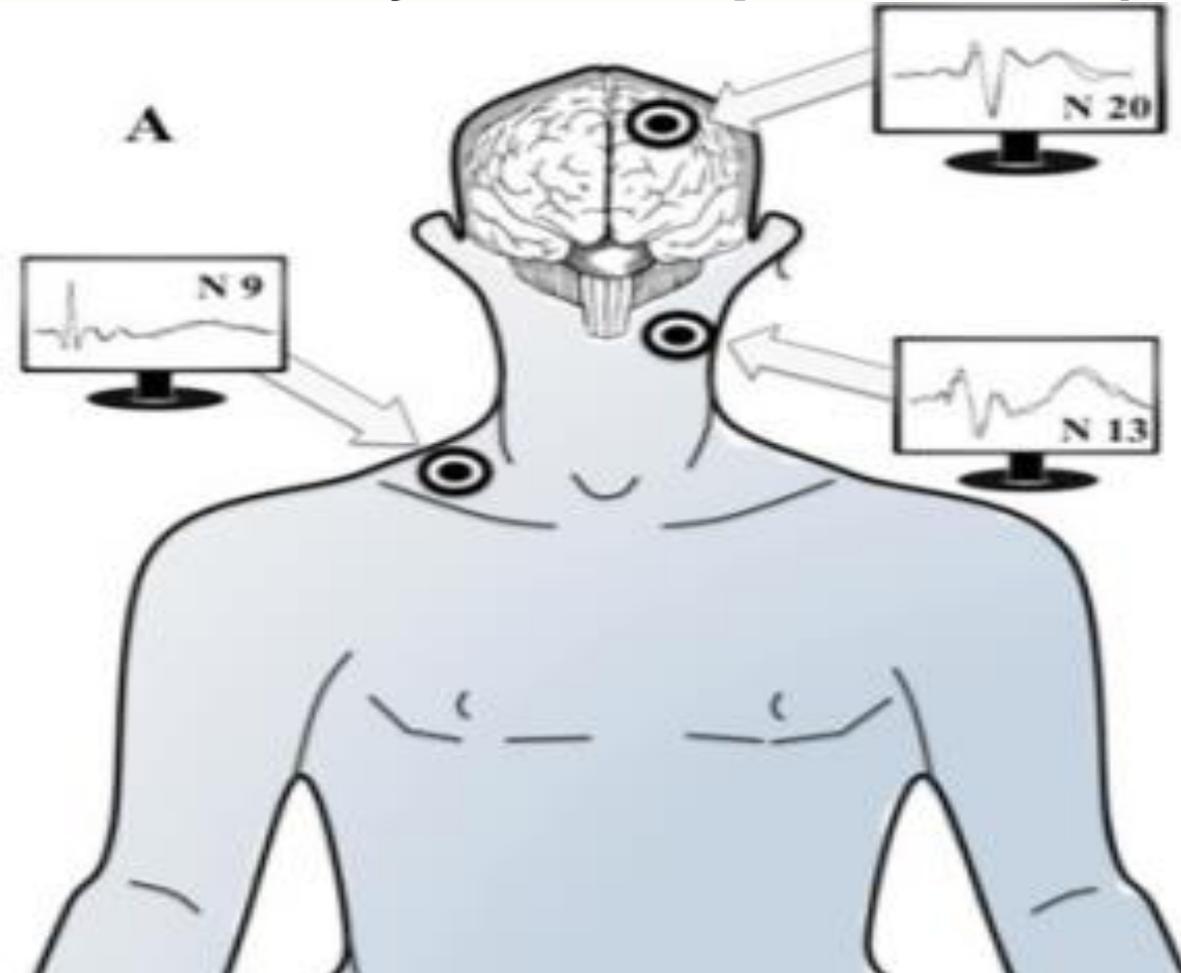
- ❖ New approaches using non-strict resting-state EEG might provide new perspectives for finding physiological features that may contribute to diagnoses.
- ❖ Standard EEG patterns in DOC patients showed a difference between the MCS and VS in sleeping states.
- ❖ The occurrence of EEG patterns, including sleep spindles, slow wave activity, and the variability of brain rhythms (theta, alpha, and beta), were demonstrated to have significant correlations with the patients' behavioural diagnoses.
- ❖ The detection of blink-rated oscillations contributed to the differential diagnoses between the MCS and VS.

Resting-State Electroencephalography in Disorders of Consciousness

The EEG Analysis for Diagnosis:

- ❖ Blink-related delta oscillations linked with awareness of the surrounding environment, which is a criterion for assessing consciousness.
- ❖ The detection of blink-related activity differs from the classical resting-state measurement. However, although it included an event input, the resting-state blinking is also a type of spontaneous activity, differ from external stimulus used in ERP.

Somatosensory evoked potentials (SEP)



Somatosensory evoked potentials (SEP)

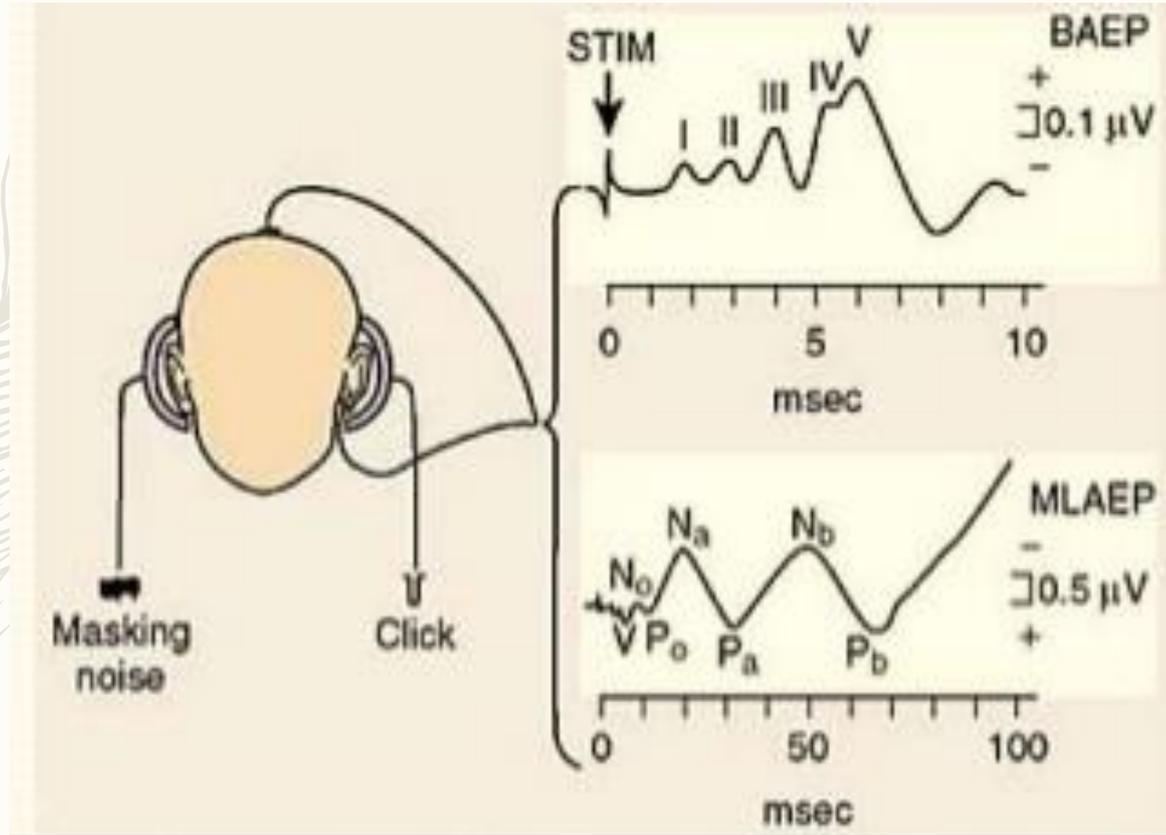
- ❖ Somatosensory evoked potentials (SEP) are elicited by sensory electrical stimulation of the median nerve at the wrists.
- ❖ Bilateral absence of SEPs in coma patients is strongly related with unfavourable outcome especially in patients with hypoxia–ischemia aetiology.
- ❖ A large scale review including 2891 patients can be consulted (Robinson and Micklesen, 2014).
- ❖ All patients with good outcome have developed normal SEPs but they are also present in patients with unfavourable outcome.

Visual evoked potentials

- ❖ Visual evoked potentials, elicited using flashing LEDs, are less used at the intensive care because these are not systematically present even in healthy subjects.



Brainstem auditory evoked potentials (BAEP)

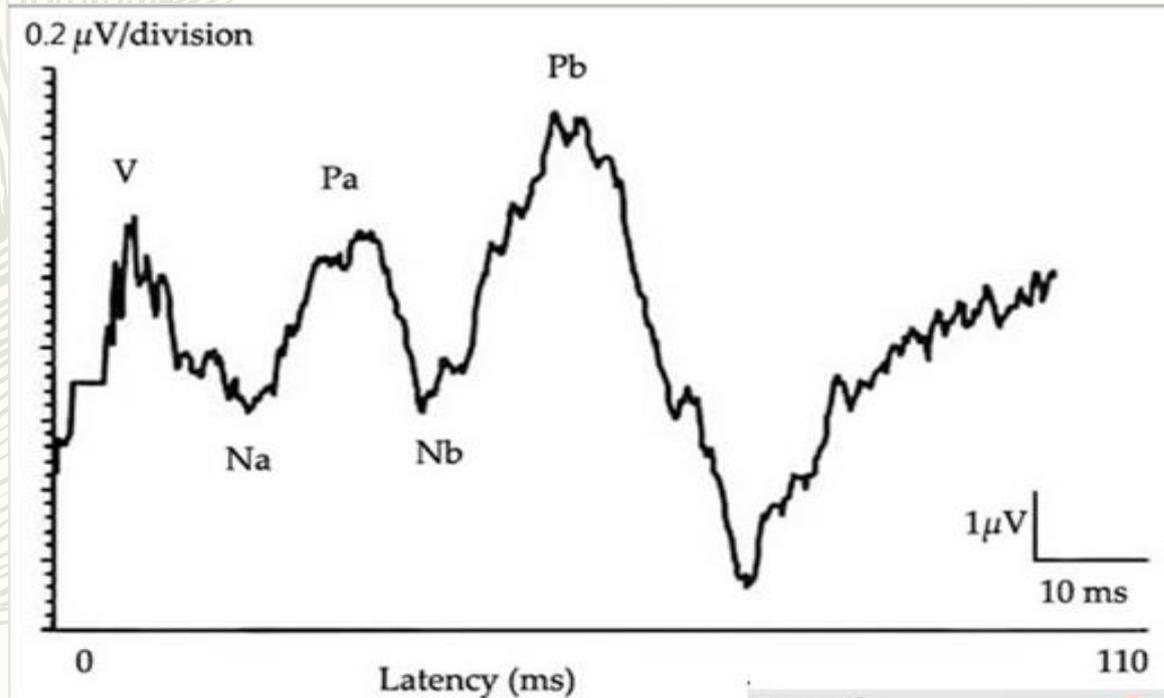


Brainstem auditory evoked potentials (BAEP)

- ❖ Brainstem auditory evoked potentials (BAEP) are most often used with sounds (“clicks”) using headphone.
- ❖ They are evoked in the first 10ms revealing the activity from the auditory nerve to the inferior colliculus.
- ❖ The absence of BAEPs is also a reliable marker of bad outcome when there is no evidence of peripheral auditory injury.
- ❖ However, the presence of normal BAEPs does not indicate a good outcome.

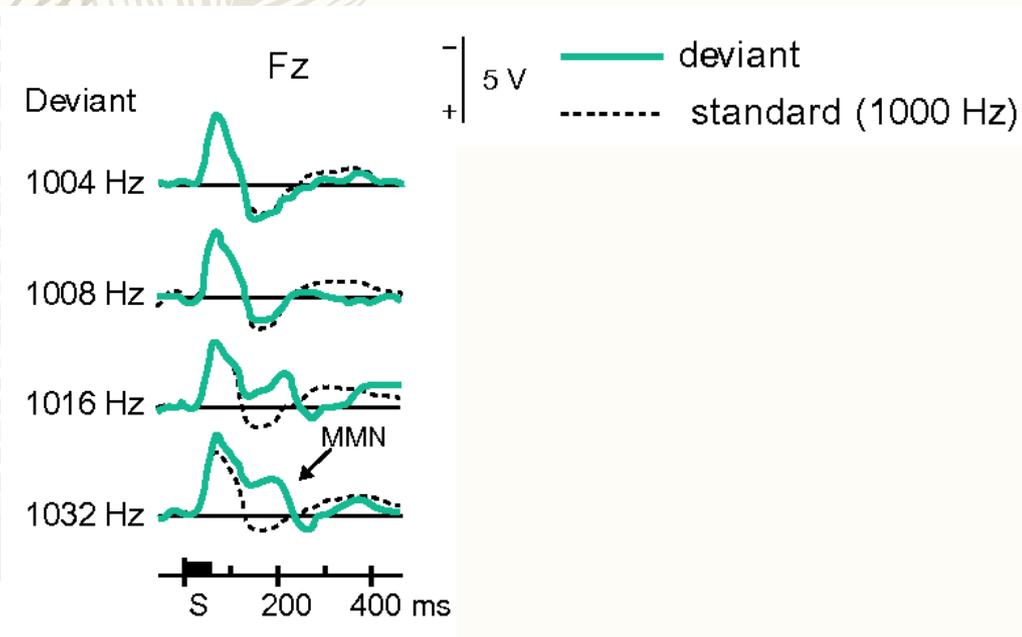
Middle-latency auditory-evoked potentials (MLAEP)

- ❖ Middle-latency auditory-evoked potentials (MLAEPs) appearing between 10 and 50 ms and possibly related to the activation of primary auditory cortex and thalamus is strongly associated, when absent, with poor outcome in post-anoxic coma.

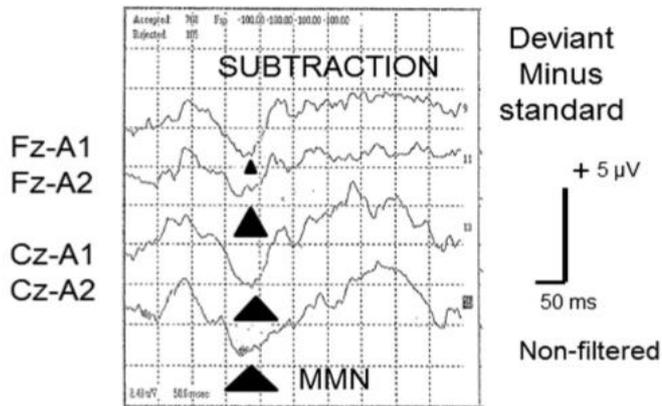
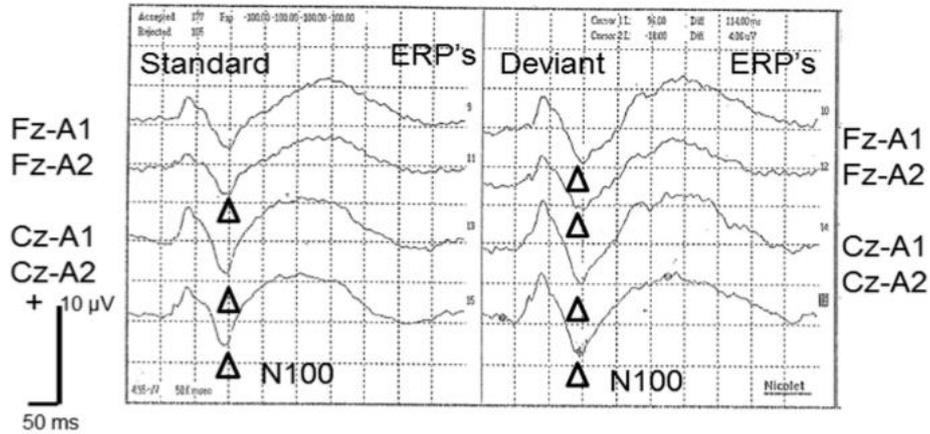


Mismatch negativity (MMN)

- ❖ The mismatch negativity (MMN) is a pre-attentive auditory event-related potential (ERP) component that is elicited by a change in a repetitive acoustic pattern. It is obtained by subtracting responses evoked by frequent 'standard' sounds from responses evoked by infrequent 'deviant' sounds that differ from the standards along some acoustic dimension, e.g., frequency, intensity, or duration, or abstract feature.

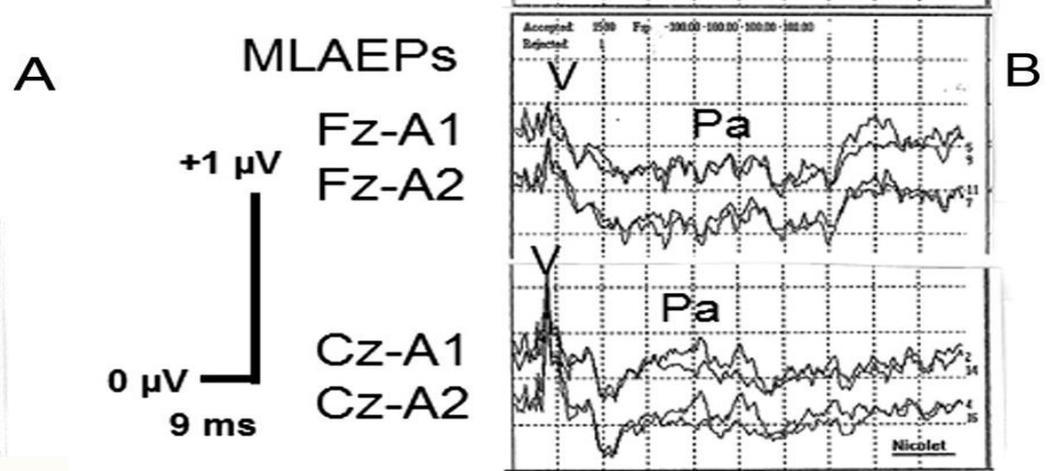
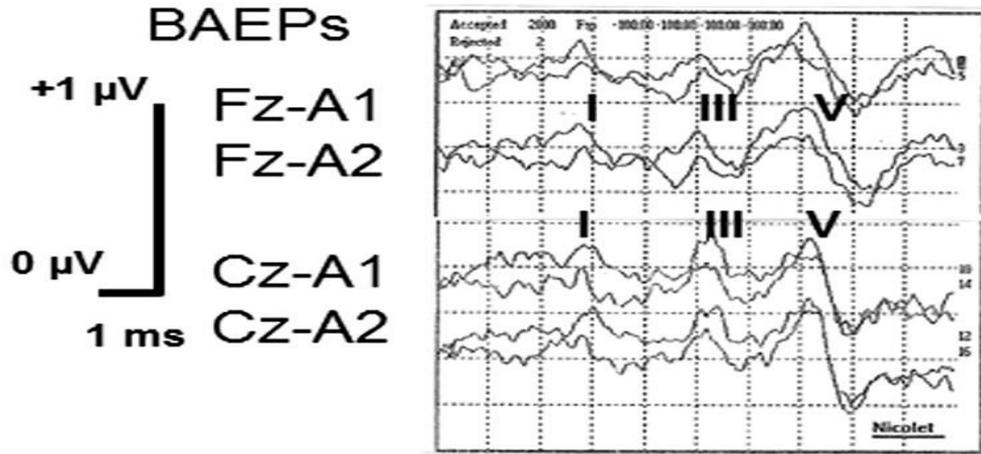


Can auditory-evoked potentials improve our prediction of awakening in comatose patients?

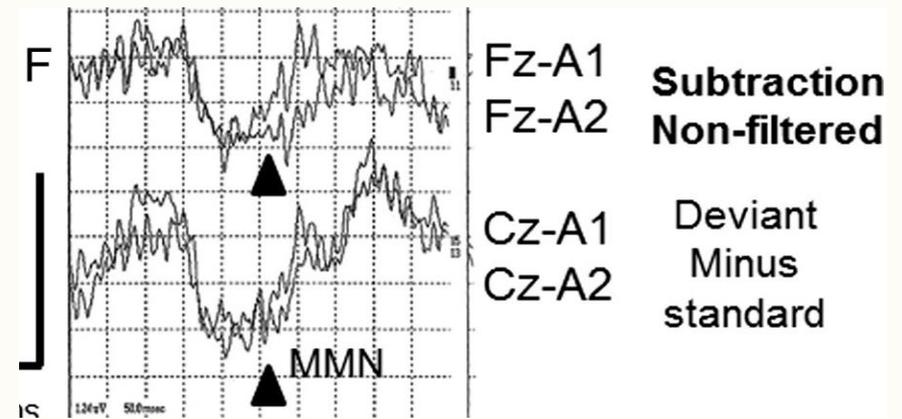
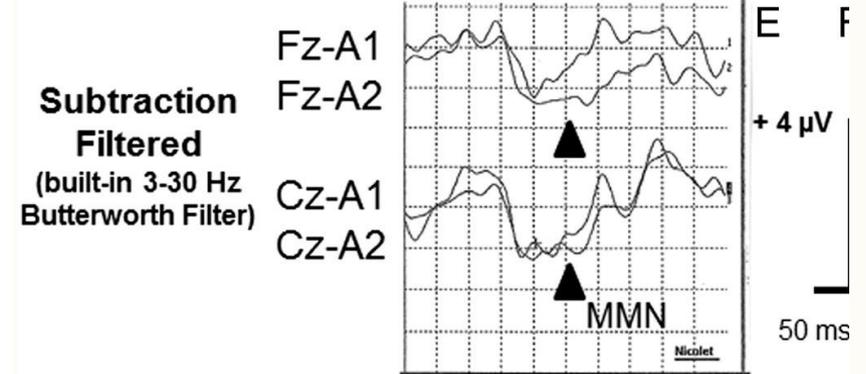
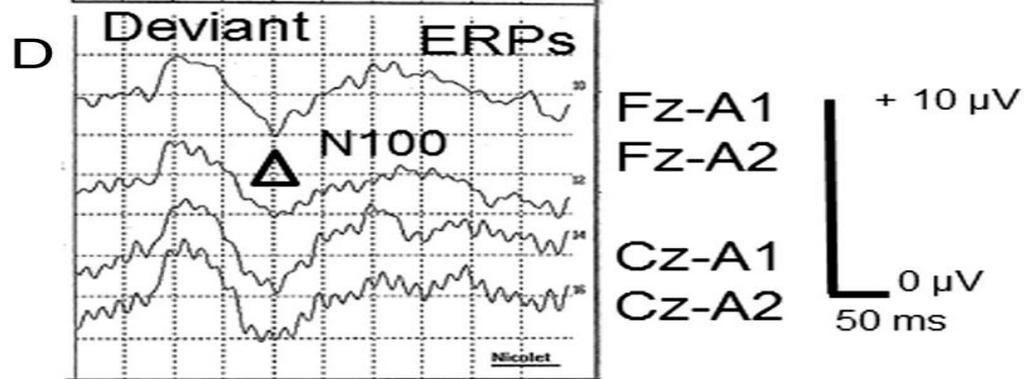
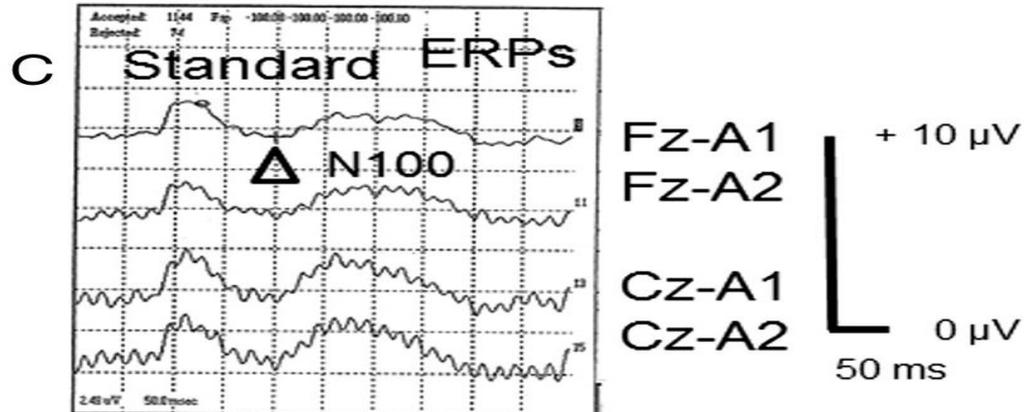


- ❖ Event-related potentials to standard and deviant acoustic stimuli recorded 3 days after CABG in a 60-year-old man. Event-related potentials were taken with the patient asleep.
- ❖ The upper panel displays the ERP waveforms to the standard and deviant stimuli and their corresponding N100 waves (unfilled triangles).
- ❖ The subtracted responses show a clearly distinctive mismatch-negativity (MMN) (filled triangles).

A 66-year-old man with chronic renal insufficiency was in coma because of a global anoxic-ischemic and metabolic encephalopathy after resuscitation from cardiac arrest during a percutaneous coronary intervention. He was treated with hypothermia for 24 hours. A non-contrast head CT-scan showed no evidence of diffuse ischemia.



- Auditory-evoked potentials performed in the absence of sedation (36 hours) 5 days after coma onset demonstrated waves I, III, and V from the BAEP (A) and a Pa wave (B) with normal configuration.



- Event-related potentials showed an N100 wave to both the standard and deviant stimuli (D; unfilled triangles), whereas the subtracted waveforms (F: unfiltered; panel E: filtered) displayed an MMN (filled triangles).
- The presence of MMN was suggestive of awakening, and the patient regained consciousness 9 days after evoked potential examination. The Glasgow-Pittsburgh Cerebral performance score at the time of discharge was indicative of moderate disability (score of 2).

Study done by Rodriguez et al published in the Journal of Critical Care in 2016

BAEPs:

- ❖ Brain stem AEPs were present bilaterally in all awakened patients in response to the stimulation of the left and right ears and were also recorded bilaterally in 80% (8/10) and unilaterally in 10% (1/10) in the patients who did not.
- ❖ All awakened patients had a clearly distinctive Pa wave of the MLAEPs bilaterally (7/7), and it was also present bilaterally in 30% (3/10) and unilaterally in 20% (2/10) in non awakened patients.
- ❖ In all 7 patients from the coma group (100%) who recovered consciousness, BAEPs were classified as grade 1 (normal configuration), but in those who did not, 5 patients (50%) had BAEPs classified as grade 1, 4 (40%) as grade 2 (increase in the I-V interval but no decrease in wave V amplitude), and 1 (10%) as grade 5 (only wave I detected).

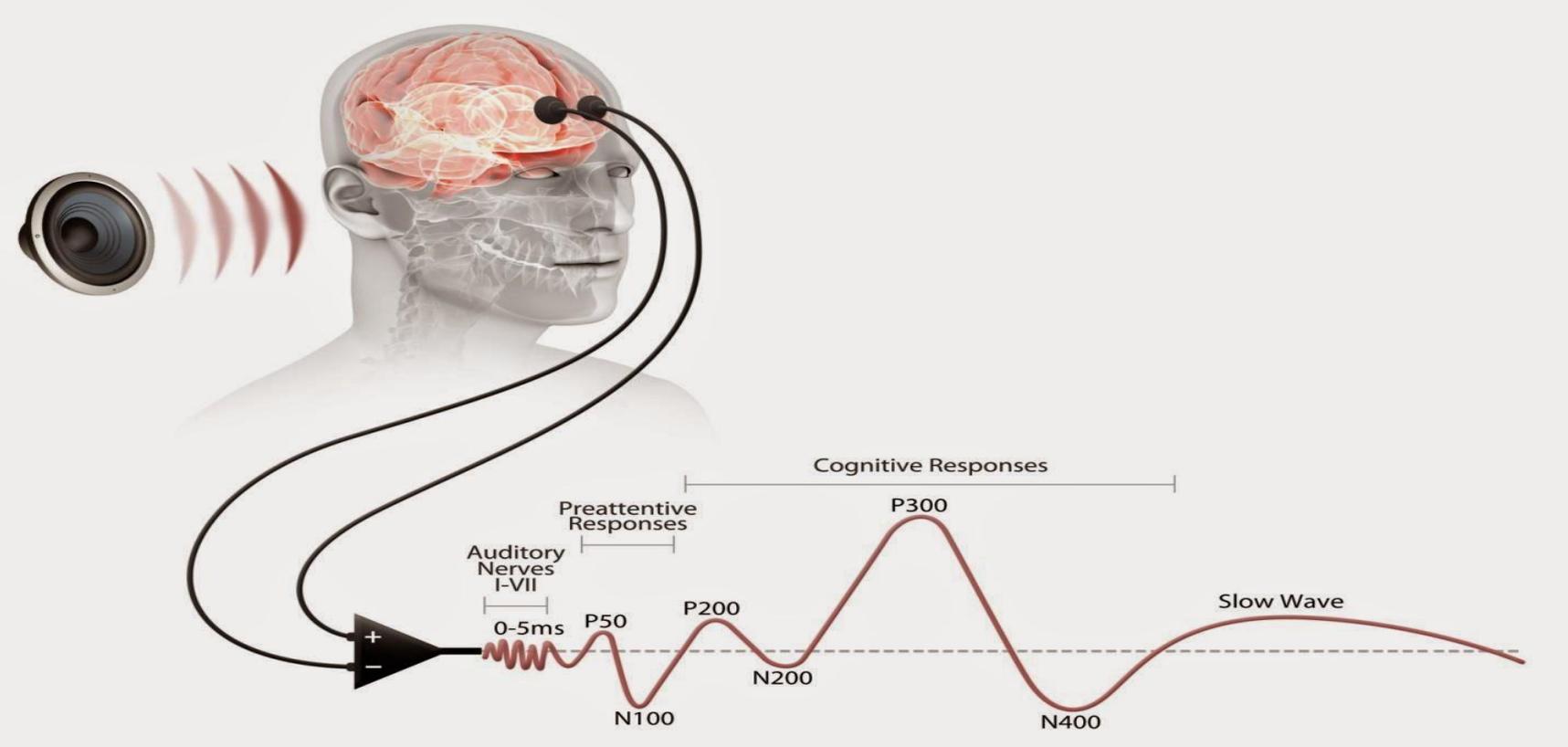
Study done by Rodriguez et al published in the Journal of Critical Care in 2016

MLAEPs:

- ❖ Middle-latency AEPs were classified as grade 1 (normal configuration) in all patients who awakened from coma.
- ❖ However, in non awakened patients, only 2 (20%) were classified as grade 1, 1 (10%) as grade 2 (delayed Pa wave, but its amplitude was greater than $0.3\mu\text{V}$), and 7 (70%) as grade 4 (no Pa wave detected).
- ❖ All patients in the control group had intact BAEPs.

Study done by Rodriguez et al published in the Journal of Critical Care in 2016

ERPs:



Study done by Rodriguez et al published in the Journal of Critical Care in 2016

ERPs:

- ❖ The N100 waves to standard and deviant stimuli were identified in all patients from the control group but in only 12 of the comatose patients (71%).
- ❖ The subtracted responses showed MMN in all patients from the control group and in only 9 (53%) of the 17 comatose patients.
- ❖ The MMN in comatose patients was never observed in the absence of standard and deviant N100 waves, but there were 3 patients who had small N100 waves in the standard and the deviant response so that no MMN was generated in the subtracted response.

Study done by Rodriguez et al published in the Journal of Critical Care in 2016

ERPs:

- ❖ The 3 patients with N100 waves but no MMN did not recover consciousness.
- ❖ In addition, we found that the MMN of patients in coma showed longer latencies (192 ± 46 milliseconds) and reduced amplitudes ($2.2 \pm 0.9 \mu\text{V}$) compared with controls (latency: 160 ± 36 milliseconds; amplitude: $2.6 \pm 1.2 \mu\text{V}$), but their differences were not statistically significant.

Study done by Rodriguez et al published in the Journal of Critical Care in 2016

- ❖ At the time of discharge, 43% (3/7) of the patients who recovered consciousness were classified with moderate disability (score 2) and 57% (4/7) with severe cerebral disability (score 3) by the Glasgow- Pittsburgh Cerebral-Performance Category scale.

| | |
|-------------|--|
| CPC level 1 | Normal ability or minimal disability (good cerebral performance, conscious, alert, able to work, and lead a normal life) |
| CPC level 2 | Moderate cerebral disability (conscious, sufficient cerebral function for part-time work in a sheltered environment or independent activities of daily life. May have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes). |
| CPC level 3 | Severe disability (conscious, dependent on others for daily support because of impaired brain function) |
| CPC level 4 | Severe disability (coma, vegetative state, no cognition, verbal or psychological interactions with the environment) |
| CPC level 5 | Death (or brain death) |

CPC, cerebral performance category.



Study done by Rodriguez et al published in the Journal of Critical Care in 2016

- ❖ A score of 5 was given to 10 comatose patients who died.
- ❖ Moderate disabilities were associated with hemiplegia and permanent memory changes.
- ❖ Severe disabilities included patients who were dependent for daily life support because of limited cognition and dementia.

Study done by Rodriguez et al published in the Journal of Critical Care in 2016

- ❖ None of the patients had any disability before this admission.
- ❖ Among patients with presence of MMN, 3 (33%) of 9 had moderate disability, 2 had severe disability (44%), and 2 were dead (22%) at the time of discharge.
- ❖ In comparison, in the 8 patients with absent MMN, all (100%) subsequently died.

Study done by Rodriguez et al published in the Journal of Critical Care in 2016

- ❖ Mis match negativity was detected in all patients who recovered consciousness and in only 2 (20%) of those who died without regaining consciousness.
- ❖ None of the patients with an absent MMN recovered consciousness.
- ❖ We found that all patients who awakened had intact BAEPs, Pa, and N100 waves compared with 90%, 50%, and 50%, respectively, in non awakened.
- ❖ This suggests that the identification of N100 alone does not guarantee the presence of MMN. In contrast, it appears that intact functioning of the brain stem and cortical areas involved in the recording of BAEPs and MLAEPs is essential for the recovery of consciousness because all awakened patients had normal BAEPs and Pa waves.
- ❖ However, specificity of BAEPs and MLAEPs for predicting awakening is poor.

Clinical application of evoked and event-related potentials

- ❖ The bilateral absence of short latency cortical potentials is very nearly 100% specific for prediction of a poor outcome (defined as death or persistent vegetative state) after hypoxic ischaemic and intracranial haemorrhagic insults, but is slightly less predictive after traumatic brain injury (TBI), particularly in children.
- ❖ A study published by Dr. Nick Kane showed that after TBI as many as 12 patients out of 777 had favourable outcomes (good or moderate disability) despite bilaterally absent SSEPs. This observation has been detailed in a number of case reports of patients making good recovery after both anoxia and TBI, where barbiturate coma or raised intracranial pressure may have contributed to the loss of cortical responses.
- ❖ The predictive value of SSEPs is superior to clinical tests and can be predictive of a poor outcome even when brain stem function is preserved after anoxia.

Evoked Potentials and the Prognosis of Comatose Patients Receiving Intensive Care

- ❖ The American Academy of Neurology has endorsed the use of SSEPs (with a level B rating) in a decision algorithm for prognostication of comatose survivors after successful cardiopulmonary resuscitation.
- ❖ Although the absence of short latency responses is a poor prognostic feature, their presence does not guarantee the return of consciousness or survival, and we must look to other electrophysiological probes as well.
- ❖ Long latency event related potentials (ERPs) have been the subject of several reviews and the findings of one meta-analysis are now known.

Evoked Potentials and the Prognosis of Comatose Patients Receiving Intensive Care

- ❖ This analysis pooled data from 10 studies of patients in coma and other low responsive states (GCS <12) of various aetiologies in order to estimate the predictive power (odds ratio, OR, and its confidence limits, CI) of several ERPs measures.
- ❖ Since the greater the value of the OR (or more precisely the lower limit of its CI) indicates that presence of the ERP component is a significant predictor of awakening, the P300 would seem to be the test of choice. Indeed P300 was the original ERP component reported in four patients who recovered from traumatic coma,¹⁹ which was subsequently confirmed in a large cohort.

Since the greater the value of the OR (or more precisely the lower limit of its CI) indicates that presence of the ERP component is a significant predictor of awakening, the P300 would seem to be the test of choice. Indeed P300 was the original ERP component reported in four patients who recovered from traumatic coma, which was subsequently confirmed in a large cohort.

Table of Odds Ratio with Confidence Intervals (CI) for prediction of survival by various Event Related Potential (ERP) components from pooled data.

| <i>ERP component</i> | <i>Odds Ratio (OR)</i> | <i>95% CI</i> | <i>Patient Number</i> |
|-----------------------------|-------------------------------|----------------------|------------------------------|
| <i>N100</i> | <i>2.85</i> | <i>1.91-4.27</i> | <i>548</i> |
| <i>MMN</i> | <i>6.53</i> | <i>3.55-12.01</i> | <i>470</i> |
| <i>P300</i> | <i>8.79</i> | <i>4.88-15.83</i> | <i>313</i> |

Evoked Potentials and the Prognosis of Comatose Patients Receiving Intensive Care

- However, MMN is an automatic process in both sleep and wakefulness whilst P300, in the awake state at least, is modulated by arousal and attention, which clearly can be neither controlled nor assessed in an unresponsive patient.
- It was largely this potential confounding factor that encouraged investigators to assess the automatic pre-attentive MMN auditory novelty detection mechanism, and which may account for its apparent greater specificity (91% versus 77% for P300).
- The presence of MMN has been shown to be predictive of awakening from both acute traumatic and non traumatic coma, and the vegetative state.

Conclusion

- There is evidence that both evoked and event related potentials could help refine clinical predictions of outcome from coma.
- It is fair to say that evoked potential recordings are reliable predictors of poor outcome and are inexpensive, non-invasive tests that can be safely recorded at the patient's bedside.
- The neurophysiologist needs experience to be aware of certain caveats in their clinical application.

Conclusion

- ❖ Clinical Neurophysiology departments across the country regularly record EEGs in Intensive Care Units, but very few ever record evoked potentials, and even less recording them on a fairly frequent basis.
- ❖ Although in their infancy event-related potentials have shown some promise in heralding awakening and favourable neurological prognoses, and can therefore complement evoked potentials.
- ❖ ERPs are more complex in both their recording technique and interpretation, and will require further evaluation before clinical utility can be achieved.



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The Best Medicine

THIS PATIENT WAS ADMITTED FOR OVER-EXHAUSTION... SEEMS LIKE HE WORKED ALL THROUGH THE HOLIDAY SEASON WITH NO TIME OFF!

SOUNDS LIKE HE WORKS THE SAME HOURS AS A Neurophysiologist

