NEUROPHYSIOLOGICAL SIGNS OF BRAIN DEATH
(EEG & EVOKED POTENTIALS):
ARE THEY SAFE & RELIABLE?

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ElectroEncephaloGraphy (EEG) was introduced by Hans Berger in the 20s and 30s. This technique allowed for the first time to record from the scalp the electrical activity of a living brain. The signal picked-up via surface electrodes reflects the sum of the post-synaptic potentials of the underlying cortical neurons. In order to increase the signal-to-noise ratio (neurons produce very small electrical signals in the order of microVolts, that is a million times smaller than 1 Volt!) differential amplifiers were created – that is amplifiers which make an electronic subtraction of the signals entering grid 2 from those entering grid 1 at the same instant (if they are of the same polarity they go therefore to 0, while if they are of opposite polarity they double in amplitude) – with the need of having two different electrodes (one exploring and one referential) for each explored brain region which corresponds to one recording channel. In order to cover simultaneously the whole brain surface, multichannel EEG machines have been developed up to 250 channels of the modern ones utilized for research purposes. However, for clinical applications, 8 to 16 recording channels are routinely employed.

Since pioneering days, it was shown that the EEG signal is quite sensitive to the state of the neural cells producing it: moreover, it was shown that complete deprivation of blood flow provokes in a few minutes the rapid deterioration of the EEG signal, followed by electrical failure and cell death with complete electrical silence. In the 50s French researchers clearly demonstrated that in comatose patients with complete brain destruction the EEG was isoelectric or flat. When this EEG pattern was present for a sufficiently prolonged time, prognosis for survival was unfavourable.

In the following years the concept of brain-death clinical condition was progressively introduced and it was demonstrated that – when present – it is invariably associated to an isoelectric, flat EEG pattern.

* The views expressed with absolute freedom in this paper should be understood as representing the views of the author and not necessarily those of the Pontifical Academy of Sciences. The views expressed in the discussion are those of the participants and not necessarily those of the Academy.
One should remember that EEG records the spontaneous bioelectrical activity of the cerebral cortex to a depth of about 5 mm without information from the brain stem. Meanwhile, following about 8 min. of complete anoxia due to circulatory arrest – as it happens with the increasingly higher intracranial pressure of post-traumatic severe coma leading to brain death condition – EEG becomes irreversibly isoelectric and is a reliable test of brain death.

However, the clear identification of an isoelectric EEG is not an easy tool. Electromagnetic fields in the ICU can pose difficulties for artefact-free traces and the EEG is very sensitive to sedative drugs hypothermia and metabolic abnormalities; all these conditions can approach the isoelectric EEG pattern, despite a still vital brainstem. Blood levels of seda-
tive drugs and metabolic conditions must therefore be tested before the EEG examination can be interpreted safely.

Moreover, isoelectric EEG condition is reached progressively through different EEG stages in which the electric signal is deteriorating, finally becoming extremely low-volted, until it disappears completely. Therefore, in order to exclude any residual EEG activity, long-distance montages and amplifiers with a ‘gain’ of at least 2 microV/div. must be employed. Artefacts from environment (i.e. mains, ventilator shock and endo-tracheal tube vibrations, neon lights etc.) and from non-brain generated biological signals (i.e. EKG) can resemble spontaneous EEG activity and should be interpreted only by skilled and trained (possibly certified) personnel. EEG reactivity to external stimuli and to transient disconnection from the ventilator in monitored conditions (i.e. following standards for the apnea-test) should also be evaluated. However, even when the best skills are adopted, up to 20% of either false or positive pitfalls affect EEG recordings for brain-death diagnosis.

![Brain death: EEG](image)

Fig. 2. Isoelectric or flat EEG in a brain-death condition. Notice the high sensitivity of amplifiers (2 uV) and the long distances of recording electrodes.
**EEG**

In BD condition it must be demonstrated a ‘flat’ (isoelectric) EEG—namely the absence of any spontaneous or provoked electric brain activity—with an amplitude exceeding 2 μVolt on any scalp region for a continuous epoch of at least 30".

![Isoelectric EEG pattern](image)

**Fig. 3.** Isoelectric EEG pattern due to brain-death condition notice the presence of rhythmic artefacts of biological origin due to EKG volume spread to the scalp recording electrodes.

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**MINIMAL TECHNICAL STANDARDS FOR EEG RECORDING IN SUSPECTED BRAIN DEATH** (Daly and Pedley 1990)

1. Minimum of 8 scalp electrodes and 2 earlobe reference electrodes following an initial study using all 21 electrodes of the 10-20 system
2. Interelectrode impedances under 10 000 but over 100 Ω
3. Tests in integrity of the entire recording system
4. Interelectrode distance of at least 10 cm
5. Instrumental sensitivities of 2 μV/mm for at least 30 min
6. Low- and high-frequency cutoffs must be no higher than 1 Hz and no lower than 30 Hz, respectively
7. Monitoring of artifacts, especially the electrocardiogram, and elimination of EMG artifacts by neuromuscular blocking agents
8. Tests of EEG reactivity to intense noxious, auditory, and, whenever possible, photic stimuli
9. Performance of the record by a qualified technologist experienced in recording EEGs in intensive care units and working under the supervision of a qualified electroencephalographer
10. Repetition of the whole test after an interval (e.g. 6 h) whenever electrocerebral inactivity is doubtful
In the late 1960s and in the following two decades, the progressive introduction of computers for analog-to-digital conversion of biological signals allowed to record *stimulus-related Evoked Potentials*; they were mainly based on electronic devices performing mathematical averaging of brain responses triggered by external (i.e. visual, acoustic, somatosensory) stimuli and analog-to-digital transformed signals via appropriate sampling rates. After such and electronic averaging and a sufficient number of repetitions, all the EEG waves which had a precise chronology with the stimulus tended to 1, while all the EEG activities (both biological and artefactual in origin) randomly occurring, without any precise stimulus-related chronology tended to 0. This method allowed to improve the signal-to-noise ratio at a level that also peaks at submicrovolt amplitude could be disentangled from background noise of higher amplitude. Individual waves of stimulus-related Evoked Potentials were labelled either with letters indicating their polarity (P for positive, N for negative) followed by their modal latency in the control population (i.e. P14 for a wave of Positive polarity and a modal latency of 14 milliseconds) as it was for the Somatosensory Evoked Potentials (SSEPs) or with roman numbers (I to VII) as it was for Acoustic Brainstem Responses (ABR). A bulk of experimental evidences either in animal models or in humans following focal lesions, allowed for the anatomo-functional description of the generator source(s) for individual peaks.

As far as ABR is concerned it was clearly demonstrated that wave I and the early part of wave II are generated from the eight nerve in its extracranial trajectory, while the latter part of wave II and the following waves are entirely generated within the brainstem acoustic pathways and relays from cochlear nuclei to lateral lemniscus, inferior colliculus and trapezoid body.

As far as SSEPs are concerned, it was found that – by using the appropriate reference electrode positioning on a non cephalic site or on the earlobe – both far-field waves (generated within the brachial plexus = P9, cervical dorsal roots and dorsal horn = P11, brainstem medial lemniscus, gracile and cuneate nuclei = P13-14) and near-field waves (generated in the thalamocortical projections i.e. = N18, and postcentral primary somatosensory cortex = N20) can be reliably recorded.

The diagnosis of brain death often uses median nerve somatosensory evoked potentials (SSEPs) or auditory brainstem responses (ABRs) which have been repeatedly and reliably shown to disappear when the clinical signs of this condition are evident. In fact, the progressive loss of the intracranially generated waves of ABR (namely waves II to V) in serially
executed recordings, confirm the loss of function of the acoustic pathways in the brainstem. Similarly, in median nerve SSEPs the progressive loss of waves N20, N18, P13-14 are reflecting the rostro-caudal deterioration of the sensory relays and tracts from the primary somatosensory cortex to the brain stem. Such electrophysiological patterns fit well with the clinical signs of brain death.

Evoked-potential testing (like EEG recording) is non-invasive and not painful for patients and can be performed at bedside by specialized personnel. It is worth recalling that these types of brain responses – at great difference from EEG signals – are virtually independent from the effects of sedative medications.

ABR responses compatible with brain-death diagnosis are clearly showing only wave I and sometimes the early part of wave II.

Fig. 4. From traces 1 to 9 we have individual EEG responses to individual external stimuli at the instant of the vertical arrows. Such traces contain both stimulus-related peaks and non-stimulus-related peaks which are randomly occurring. Following averaging procedures (bottom trace) only the stimulus-related response is clearly evident, while all the other trace deflections go to zero.
Fig. 5. ABR recordings during monaural acoustic stimuli with clicks delivered via headphones. The non-stimulated ear is masked with white noise. Note in the traces the peaks with Roman numbers from I to VI, which are all generated in the brain stem.

Fig. 6. ABR in brain-death condition. Notice that only wave I (generated within at the eighth nerve level) is elicited by the stimuli of either ear.
Median nerve SSEPs in brain-death conditions are typically limited to waves P9 and P11, while all the following waves are missing. When a P13-14 peak is still present, one can safely maintain that the brainstem is still functioning.

Fig. 7. Median nerve SSEPs in a comatose subject. On the top responses from the brachial plexus, 2nd from top cervical cord-roots responses, 3rd & 4th scalp responses. The presence of the P13-14 suggests that in this case the brain stem is still functioning.

Fig. 8. Median nerve SSEPs in a comatose subject. Traces have been recorded before (left column) and after (right) brain death condition became clinically evident. Wave P14 disappears in the BD condition.
When matching EEG with Evoked Potentials for brain-death determination several main advantages of the latter with respect to the former can be clearly seen: their relative insensitivity to environmental noise with a higher signal-to-noise ratio (due to averaging procedures), a straightforward assessment of brainstem function, their relative insensitivity to sedatives and neuromuscular blockers. Meanwhile, two main limitations should be recognized: they only explore sensory pathways and remain entirely normal in the presence of selective motor pathways derangement (however, modern techniques for transcranial magnetic stimulation of corticospinal fibres and spinal roots can easily circumvent such a limitation), they can be – as already stated in the main text – severely affected or totally missing because of lesions outside the brainstem and CNS (i.e. cochlear damage, 8th nerve lesion within the temporal bone, spinal cord or brachial plexus or peripheral nerve traumatic avulsion).

In conclusion, the following points might be outlined:

- Neurophysiological methods should be considered an extension of the clinical examination
- They are safe, reliable, non-invasive and cheap
- They are not sensitive to muscle blockers and – when EEG is combined with Evoked Potentials recording – to sedatives and metabolic agents
- Instead of being considered redundant, they might actually increase diagnostic safety. A combination of EEG, short- and middle-latency EPs is probably conveying the most reliable bulk of information on cortex and brainstem conditions (>95% of abnormalities compatible with brain-death definition).