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Editorial

# EEG-reactivity: What is it good for?

In this issue Sarah Benghanem et al. describe the Parisian registry's experience of using electroencephalographic reactivity (EEG-R) for prediction of neurological outcome after cardiac arrest in a single centre large consecutive cohort, prospectively collected and retrospectively analyzed.[1] But what is 'EEG-R' and what is it good for? EEG-R is something that even Neurophysiologists often find difficult to define consistently, although they 'know it when they see it'. Essentially it is a reproducible change in the brain's background electrical activity, visible in the on-going scalp recorded EEG, in direct response to external stimulation of an apparently unresponsive patient. Its presence implies integrity of the sensory receptors (somatosensory, eye and/or ear), their afferent fibres, subcortical and cortical generators; and that the stimulus has been perceived by a sentient brain which generates an arousal response. Hypoxic ischaemic encephalopathy (HIE) after cardiac arrest can damage these structures, with the basal ganglia and neocortex of man being particularly vulnerable, such that absence of EEG-R implies that these structures have been injured with potential neurological implications. Conversely presence of EEG-R suggests functional integrity, and therefore a potential prognostic biomarker for neurological recovery.

Clinicians looking for quick and easy answers in a complex situation, such as an unconscious post-cardiac arrest HIE patient with possible extreme outcomes, might be tempted to view such a simple bedside prognostic test as dichotomous (i.e. presence=survival and absence=death). Unfortunately, the situation is not quite so binary, and in 2014 representatives of the European Resuscitation Council and the European Society of Intensive Care Medicine wisely recommended using absence of EEG-R *only* in combination with other EEG features of poor neurological prognosis (i.e. presence of burst suppression or status epilepticus, but not a low voltage EEG).[2] Recently there have been further advances with some good quality evidence, albeit tempered by the possibility of the self-fulling prophecy bias. EEGs are now routinely performed in unconscious patients on ICU, either intermittently or continuously, for both diagnostic and prognostic purposes. One of the principle clinical reasons being that an unconscious patient may be in treatable nonconvulsive (subclinical) status epilepticus, which can in practice only be diagnosed with EEG and may occur in about one quarter of comatose survivors of cardiac arrest. It would be unethical to withhold any relevant information from the treating physician, making a randomized trial of EEG pragmatically unfeasible.

Importantly then, the Parisian group did not use EEG-R in their Withdrawal of Life-Sustaining Treatment (WLST) protocol, so its absence may not have biased their results. Indeed, this may even have facilitated their pertinent discovery that 6 patients with an initial absent EEG-R later awoke and had favorable outcomes. They postulate that sedation with midazolam might have interfered with the reactivity assessment. However, there have been case reports of the reemergence of EEG-R without the potential confounders of drug intoxication, hypothermia or sedation effect,[3] suggesting that EEG-R may in fact be a dynamic response like other electrophysiological indicators of awakening from coma.[4] These observations oppose a previous report that absent EEG-R has 100% positive predictive value with no false positives for a poor outcome.[5] Their valuable finding is akin to the observation of good outcomes in patients with early onset post-anoxic status myoclonus,[6] having previously been viewed as an 'agonal phenomena'. Reemphasizing that, as with other biomarkers, absent EEG-R should never be used alone in WLST decisions as it is insufficiently reliable, a conclusion reached in a recent prospective multicenter trial.[7]

Clinicians and neurophysiologists are rightly concerned about the potential confounding effects of sedation on EEG patterns and reactivity testing; and for the inexperienced offer a convenient way of avoiding or deferring a prognostic prediction. Indeed, the authors themselves state that the present work highlights that sedation might interfere with reactivity assessment, even though their results do not lend support to this postulation. Their specificity to predict a poor outcome by a 'non-reactive' EEG without sedation is 93.5% (95% CI 78.6–99.2) versus 92.5% (81.8–97.9) with concomitant sedation,[1] i.e. sedation is not statistically associated with absent EEG-R. We believe it is fair to say that experience has taught us that sedating agents, used at typical doses on ICU, do not sufficiently alter EEG patterns as to interfere with accurate neuroprognostication. A large prospective multicenter trial has just confirmed this clinical impression for propofol.[8] The European Resuscitation Council and the European Society of Intensive Care Medicine recommended using EEG based predictors $\geq$72 h after ROSC. Since then different groups have found that the EEG performs well in the first 24 h for predicting both poor and good outcomes.[9,10] Furthermore, recently the presence of EEG-R at 24 h was found to correlate well with a favourable outcome,[11] which also appears to be true for the Parisian registry data.

Challenges remain for EEG-R: a systematic review by Admiraal et al. found that EEG reactivity testing varies greatly and descriptions of protocols are almost never replicable.[12] EEG-R clearly needs standardization in terms of range of stimuli, their duration, the conditions under which testing is performed e.g. level and drug of sedation. Unfortunately we do not yet know the best methods for eliciting EEG-R, as even different nociceptive protocols vary in their

effectiveness at evoking it.[13] Admiraal et al. have now sought consensus amongst 'experts' from 14 countries through a modified Delphi process to act as a starting point.[14] They remain optimistic that EEG-R could be implemented in the multimodal approach to neuroprognostication after CA. Quantitative EEG techniques may help mitigate against interrater observer error, by removing the need for human visual analysis.[15] So finally, what is EEG-R good for — probably something, as it is probabilistic but not deterministic. Its 'early' presence in combination with a benign EEG is a positive prognostic sign, of which we have few in HIE, and should probably promote continued life-sustaining treatment.

## Conflict of interest

None to declare.

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