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Scientific Research

Monitoring Brain and Spinal Cord Metabolism and Function*

Pierre Pandin#, Marie Renard, Alessia Bianchini, Philippe Desjardin, Luc Van Obbergh

Department of Anesthesia & Critical Care, Erasmus Academic Hospital, Université Libre de Bruxelles, Brussels, Belgium
Email: #ppandin@ulb.ac.be, #Pierre.Pandin@erasme.ulb.ac.be

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Abstract

Monitoring the metabolism and function of the central nervous system not only is an old idea but also is a topic that is of increasing interest to the technological evolution. Beside the optimization of cerebral and spinal cord perfusion and the preservation of vasoreactivity to ensure the viability of cerebral tissues and structures, we want to know more and more about the real intimate situation of these organs in real time at the patient's bedside. To this end, several tracks have been explored during the two last decades, leading to the development of numerous concepts and the conception of various monitoring systems. One of the main problems is to characterize the respective strong points and weaknesses of those ones and to conclude regarding their individual relevance and value in current clinical practice. It is more and more clear that the combination of different categories of monitoring is a way to try to find the most valuable technological compromise, to increase the chance of prediction or of early detection of intercurrent deleterious events corresponding to the concept of multimodality. The intraoperative period and the intensive care goals and targets are appreciably different. This is the reason for the attempt to define different and distinct sets of goals and targets for the intraoperative anesthetic setting and for the intensive care unit.

Keywords

Brain, Central Nervous System Monitoring, Metabolism, Function

1. Introduction

The most accurate possible monitoring of the metabolism and function of the central nervous system (CNS) re-

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#Corresponding author.

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mains a cornerstone that is a testament to the constant technological evolution. It makes possible the more and more adapted management of the brain and the spinal cord during either more and more complex and specific-neurosurgical interventions or more and more invasive investigations in neuro-intensive care unit (Neuro-ICU). For a long time now, the concept of active neuroprotection has been developed following the successive progress in the understanding of the complex interaction between the CNS, surgery, anesthesia, and/or a possible aggression (trauma, hemorrhage, ischemia, anoxia, edema, etc.). In the past, the pioneers used several rudimentary tools (for instance, the single trace analogue electroencephalogram), but unfortunately they were not integrated into the monitoring, and were without systematization or generalization (only used on a case-by-case basis). At the beginning of the nineties, a real neuro-monitoring culture emerged, as illustrated by the book edited by Peter Sebel and William Fitch, *Monitoring the central nervous system* [1]. Then, continuous efforts led to the conception of multimodal intraoperative monitoring (IOM), supported by pioneers as the American anesthesiologist Betty Grundy [2]-[4] and the English neurophysiologist Catherine Thornton [5] [6].

2. CNS: What Is Metabolism and What Is Function?

The specific functionality of well-defined neural loops or neural networks is now appreciated and their functioning seems to be governed by a biphasic on-off model [7] too often underestimated. Anesthesiologists and intensive care unit (ICU) specialists must change their mind about a more multimodal CNS monitoring for a more realistic vision of the function. Moreover, in the ICU, all the high-tech imaging innovations can give only a time to time idea of the neurological trend of the patients with sometime a lack a possible conclusion. On the other hand, in the operating room, the use of medical imaging remains limited for only very specific situations [8]. Alternatively, CNS follow-up regarding metabolism or function at the patient's bedside would be based on the combination of specific parameters not only regarding the experience of pioneers [9] [10] but also existing recommendations [11] [12] to depict with accuracy the topographical and temporal variability of the CNS [7].

3. Early Detection for Outcome Improvement But Not Any Old How…

Beside the early claimed dimension of global or segmental CNS investigation [13] [14], the early detection of the occurrence of possible troubles or abnormal events was advocated as well [2] [15], before permanent cerebral damage. The not only theoretical but desirable description of the fundamentals of this kind of monitoring is listed in **Table 1**. Their lack of materiality, fragility (micro or nanosignals respectively in µV and nV), and sensitivity to electromagnetic disturbances make recording difficult, while the frequent intricacy between what is metabolism and what is function is not so simple to interpret [16] [17]. From a practical point of view, the neuromonitoring of metabolism and function is more and more subdivided into two distinct entities: intraoperative neuro-monitoring and neuro-monitoring in the ICU (**Table 2**) considering the goals of the monitoring, and the possible accessibility of the CNS.

4. Temporal, Topographical, and Spatial Variations: The Brain Mapping Concept

The complexity of the CNS lies probably not only in its structural complexity but also in its spatial and temporal metabolic and functional variability in either awake or comatose/unconscious patients, under anesthesia or in ICU [18]-[25]. To take that into account, neuro-monitoring has not to be too excessively simplified [26]-[28] and limited only to the forehead, as accurately described by John in his "anaesthetic cascade" [19]. Moreover, resorting to standard tools and technologies makes it easier to discuss the case with the neuro-specialists regarding the patient's management and the different options.

5. Spontaneous Activities and Evoked Answers

Regarding CNS function, one other specificity lies in the difference between spontaneous activities (as a description of the neurological ambiance) and evoked responses (as the reaction capability of the CNS to stimulation) as listed in the **Table 3**. Briefly, the clinician has to use the optimal multimodal combination of monitoring following, first, the pathophysiological target and second, the local culture and know-how, and third, the availability of the potential tools [9] [14]. The ambient signals (**Table 2**) inform directly or not about the metabolic level, more or less directly linked to the regional functional level, but are nevertheless limited by the risk to be too cumulative and not discriminant enough [29]-[32]. To bypass this problem, one solution is to map the skull

Table 1. Theoretical description of the fundamentals of the ideal multimodal brain and spinal cord metabolism and function monitoring.

Theoretical description of the fundamentals of the ideal multimodal brain and spinal cord metabolism and function monitoring
Point 1: *Global or segmental investigation of the central nervous system* (*CNS*) *with the possibility of individual adaptation following each case request*
Point 2: *Similar physiological dimension of the neurological indicators in comparison to the physiological hemodynamic or respiratory parameters—no calculation, no index*
Point 3: *Early detection of possible deterioration of neural function before definitive damage, because the sooner neural dysfunction is detected, the more reversible it is* (*usefulness of trends*)
Point 4: *Multimodality*
Point 5: *Subclinical detection of physiological or pathophysiological changes before the occurrence of major and definitive consequences to guide the earliest possible intervention to reduce and/or inverse the neural suffering, to improve the vital and functional prognosis of the patients by limiting the impact on the brain, spinal cord, or both*
Point 6: *Monitoring the versatility of either cerebral pathophysiology* (*stroke, ischaemia, haemorrhage, seizures, etc.*) *or pharmacological interaction* (*anaesthesia, barbiturates, anti-epileptic drugs, etc.*)
Point 7: *Make as much as possible the distinction between the anesthesiology and the effects of surgery on the pathophysiological process*
Point 8: *Make concrete not only CNS metabolism but also CNS function to make easier the management of anesthetised patients during the intraoperative period or comatose patients during their intensive care unit stay*
Point 9: *Apply the precepts of telemedicine and telemonitoring*

Table 2. State of the art regarding the practice of neuro-monitoring during the intraoperative period vs. in the intensive care unit, based on differences in the practical conditions of realisation, goals and requests, and central nervous system accessibility (based on the literature, reflecting the actual worldwide practice "+++" corresponds to often used and/or even recommended monitoring, "++" is sometimes used and "+" matches for an occasional use. Alternatively, "-" corresponds to the lack of substantial clinical experience corresponding often to the impossibility of use, for several technical or practical reasons).

	Intraoperative neuro-monitoring (IONM)	**Intensive care unit**
Electrophysiology		
-Electroencephalogram	+++(continuous)	+++(discontinuous)
-Evoked potentials	+++(continuous)	++(discontinuous)
Cerebral biochemistry		
-Microdialysis	-	+++
Cerebral brain oxygen		
-SjvO2	+	+++
-PbtO2	+	+++
-SctO2 by NIRS	+++	++
Cerebral blood perfusion (CBF)		
-Regional CBF (TDF)	-	++
-Local CBF (LDF)	-	+
-TCD	++	+++

Table 3. Classification of central nervous system signals into spontaneous activities vs. evoked responses.

Signals	Spontaneous	Evoked
Basic principles	*-Direct & immediate reading* *-Topographical correlation* *-Neural ambiance* *-More basic*	*-Indirect & immediate reading* (*specific treatment*) *-Anatomo-functional correlation* *-Neural state* *-More advanced*
General vs. global	*-Mapped EEG* (*cEEG, dEEG, CEEG, sEEG, qEEG, QEEG*) *-SvjO2* *-SctO2* (*NIRS*)	*-Mapped EP* (*brain or spinal cord*) *-Mapped Sct*02 (*NIRS*) *EROS*
Regional vs. segmental	*-Microdialysis* *-PbtO2* *-lCBF* *-rCBF* *-TCD& microDoppler*	*-EP* (*SSEP, AEP, VEP, etc.*)

Abbreviations: *EEG*: electroencephalogram; *cEEG*: computerised EEG; *dEEG*: digitised EEG; *CEEG*: continuous EEG; *sEEG*: simplified EEG; *qEEG* and *QEEG*: quantitative EEG; *EP*: evoked potentials; *SSEP*: somatosensory EP; *AEP*: auditory EP, *VEP*: visual EP; *SvJO2*: jugular venous oxygen saturation; *SctO2*:cerebral tissue oximetry; *NIRS*: near-infrared spectrometry; *EROS*: event-related evoked optical stimulation; *PbtO2*:brain tissue oxygen tension; *lCBF*: local cerebral blood flow; *rCBF*: regional cerebral blood flow; *TCD*: Transcranial Doppler.

surface with recording electrodes following a high enough resolution [24] [25], giving numerical or graphical trends [9] [14], useful for the early detection of potential neural degradation and to adapt the patient's management. Additionally, evoked responses can indicate the functional integrity or not of the neural networks [7] (audition, vision, somesthesia, motor function, nociception, etc.). Those ones, composed of neural loops through the different anatomical CNS levels, may help to locate the occurring problem and to assess the patient's prognosis [11]. In very disturbed and extreme conditions (brain death, deep hypothermia, etc.), the whole evoked responses are nearly completely depressed with a tremendous global decrease of CNS function, reversible or not.

6. Multimodal Neuro-Monitoring in Addition to the Usual Measurements

The combination of different neuro-parameters seems now to be logical regarding the capability to monitor the metabolism and/or the function of the brain and spinal cord, but the list of indicators to be combined is not yet fixed and depends on the specific clinical problem and situation of the patient. Moreover, the real impact on the final and the long-term outcome of neurological patients remains unclear, even if the preliminary but incomplete results seem to be interesting and convincing regarding a potential recommendation of the systematic use of neuro-monitoring [30] [31]. Monitoring of the central temperature, arterial and cerebral perfusion pressure, end tidal CO2, sequential arterial blood gas sampling, glycaemia follow-up, and, of course, monitoring of intracranial pressure (ICP) are currently recommended and always form part of CNS management, to maintain homeostasis, which indirectly preserves either the metabolism or function [33]. Therefore, multimodal neuro-monitoring must be a complement and not a replacement of what exists to achieve innovative solutions [33]. Until relatively recently, ICP remains a cornerstone in our practice when the brain is damaged [33]-[36]. Following the Monro-Kellie principle, the increase of intracranial volumes may result in brain herniation, reduction of cerebral blood flow (CBF), and of course, the rise of ICP is related to increased disability and mortality [37]. According to Treggiari's review [38], the raised but reducible ICP is associated with a three- to four-fold increase in the probability of death and/or poor neurological outcome, while a refractory ICP pattern is associated with a tremendous increase in the relative risk of death (odds ratio >100). One key point would be the aggressivity of the indications of ICP catheter insertion base on clinical (coma) and Computerized Tomography (CT) abnormality [38]. However, strong evidence seems to lack when ICP is considered to guide therapy in patients with acute brain injury [39] as illustrated by the recent Chesnut's [40] randomized controlled trial which demonstrated the lack of difference in 3- or 6-month outcomes in severe traumatic brain injury patients whose treatment was based on the ICP monitoring (strictly maintained below 20 mmHg) compared with those whose the follow-up was based on imaging (CTscan) and clinical examination without ICP monitoring. In this relatively controversial context, the spontaneous technological evolution gives to the clinicians a new opportunity to progressively monitoring the ICP by non-invasive methods as a sort of alternatives [41] [42]. The Transcranial Doppler (TCD)

derived pulsatility index [41] [43], the intra-orbital optic nerve sonography [41] [44] [45] and the distorsion-product otoacoustic emissions (DPOAEs) monitoring [46] have valuable preliminary results although insufficient for now. Despite the actual controversy, the ICP monitoring remains a key element of therapeutic strategies when it rises, even if it is not excluded to have to reevaluate its real interest during the next years leading to the publication of updated recommendations of use. Less and less on its own side; the ICP monitoring is integrated more and more into multimodal neuro-monitoring [16].

7. Electrophysiology

7.1. Electroencephalogram (EEG) and Quantitative EEG (QEEG)

More functional than metabolic, EEG measures the electrical activity related to the function of the outermost brain layer: the cerebral cortex is composed of different lobes dedicated to distinct superior functions, with metabolic and functional variations [47] [48]. The mapped QEEG is able to detect the occurrence of abnormal increases or decreases (sudden or progressive) in brain electrical activity [9] [10], clinically significant or not, in comatose, sedated, anesthetised, or awake patients. QEEG has a dual value [9] [49], to detect an increase or depression of brain electrical activity. In 50% of cases, the seizures are nonconvulsive, completely silent or have an atypical clinical presentation [50] [51] potentially resulting in an increased secondary cerebral damage [52] and tissue loss [53] if they are not detected. The prevalence of nonconvulsive seizures varies between 4% to 30% [54] and is inextricably linked to sedation and anesthesia [55]. QEEG could have a real impact on not only the management of the prophylactic antiepileptic strategy, but also the final neurological outcome [56]. Within the QEEG-derived parameters, the variability in the alpha (awake) or the delta (coma or sleep) power may be helpful and relevant for the prediction of delayed ischemia in poor-grade subarachnoid haemorrhage [57] [58], to following the evolution in severe stroke patients [59], or to improve outcome in postanoxic comatose patients or after hypothermia [60]-[63]. Nevertheless, the implementation of QEEG in practice in anesthesia or critical care is challenging, requiring an interactive collaboration between anesthesiologists, ICU specialists and neurologists making supported by education and training of the participants on the ground (medical doctors, nurses), which is made easier in recent years by the development of telemedicine [64]-[68].

7.2. Evoked Potentials

The particularity of evoked potentials rests in their capability to monitor spinal cord function and indirectly monitor its metabolism [13]. By the judicious use of electrode montage, evoked potentials may inform about nervous conduction through the whole CNS until the different cerebral cortical lobes [69]-[71]. Similarly, their analysis may be global or segmental, and they can be divided into conduction index (subcortical) and in function index (cortical), as detailed in **Table 4** and **Table 5** [72]. Used worldwide, their usual indications are listed in **Table 6** [73]-[77]. Evoked potentials are usually affected by inhalational agents [73]-[75] in their amplitudes rather than their latencies, and changes in body temperature (hypothermia), nervous tissue perfusion, oxygenation and ventilation (either oxygen or carbon dioxide), and ICP (rise) may depress them [30] [78] [79]. Nevertheless and despite these influences, the evoked potentials monitoring is very valuable, remains advanced, but is more and more associated with EEG or QEEG in clinical practice and is accepted as the gold standard [75]. On the other hand, motor evoked responses or potentials (MEPs) give information about centrifugal nervous “conduction” [76] after typically, a transcranial stimulation (TcMEP). MEPsare globally less sensitive to intercurrent factors and particularly to the impact of anesthetic drugs making them a strong functional monitoring used during spine and spinal cord surgery. MEP monitoring provides excellent specificity and sensitivity whenever the motor tracts are involved in the pathological process, particularly in trauma medicine. The actual recommendation is to combine TcMEP monitoring electrophysiological modalities [75].

8. Microdialysis

Only cerebral microdialysis (MCD)provides brain metabolism monitoring, because it reflects the biochemistry (glucose, lactate, pyruvate, lactate/pyruvate ratio, glutamate, urea, and anecdotal aspartate) of the cerebral tissue where the specialised catheter tip is implanted, giving an idea of the composition of the extracellular fluid [80], the adequacy of the brain energy supply, and cellular function. During cerebral ischaemia, an elevated lactate/pyruvate ratio with an elevated glutamate and a low glucose indicate cellular hypoxia [81]. These metabolic

Table 4. Evoked potential-derived subcortical index of conduction [58].

Level of brain-stem lesion	SEPs	MLAEPs	BAEPs
1. MIDBRAIN	*Normal* P14 N20 *delayed or absent*	*Abnormal*	*Normal*
2. PONS	*Normal* P14 N20 *delayed or absent*	*Abnormal*	*Abnormal*
3. MEDULLA	*Absent* P14 N20 *delayed or absent*	*Normal*	*Normal*

***SEPs*:** somatosensory evoked potentials; ***MLAEPs*:** midlatency auditory evoked potentials; ***BAEPs*:** brainstem auditory evoked potentials.

Table 5. Evoked potential-derived cortical index of function [58].

Index of Global Cortical Function (IGCF)	VEPs	SEPs
Grade 0	*Normal*	*Normal*
Grade 1	*Delayed peak III Peak VII present*	*Normal N*20, *P*24, *P*27 *N*30 *present*
Grade 2	*Delayed peak III Peak VII present*	*Normal N*20, *P*24 *N*30 *basent*
Grade 3	*Delayed peak III*	*Normal N*20
Grade 4	*No reproducible VEPs ERG present*	*P*14 *present*

***VEPs*:** visual evoked potentials; ***SEPs*:** somatosensory evoked potentials; ***ERG*:** electroretinogram.

Table 6. Classical applications of sensory evoked potentials.

Classical applications of sensory evoked potentials (EPs) during the intraoperative period and/or intensive care unit stay
Somatosensory EPs
1) Invasive spine (arthrodesis) and spinal cord surgery for detection of either medullary or radicular syndrome (combined with motor EPs and/or evoked EMG)
2) Normothermic thoracic and thoracoabdominal aortic surgery for detection of cord ischaemia (compromised vascular supply—radicular anterior Adamkiewicz artery—combined with motor EPs)
3) Deep or intermediate hypothermia for neurosurgery (cerebral vascular bypass), cardiac, or major vascular surgery (combined with motor EPs)
4) Carotid endarterectomy (alternative to mapped EEG and QEEG, because less pharmacologically depressible)
5) Surgical peripheral nerve release (surgery guidance—possibly combined with motor EPs)
6) Post-anoxic comatose patients (prognosis dimension—outcome prediction)
7) Hypothermic comatose patients (prognosis dimension—outcome prediction)
8) Spinal cord post-trauma status (combined with motor EPs and/or evoked EMG)
Auditory EPs (short or midbrain latencies)
1) Intra and extracranial surgery of the auditory and/or the facial nerves (combined with facial evoked EMG—specific facial nerve monitoring)
2) Midbrain and/or spinal cord post-trauma status (combined with motor EPs and/or evoked EMG)
Auditory EPs (middle or early cortical latencies)
1) Post-anoxic comatose patients (prognosis dimension—outcome prediction)
2) Hypothermic comatose patients (prognosis dimension—outcome prediction)
Auditory EPs (long or late cortical latencies)
1) Postoperative, post-lesion, or post-trauma cognitive dysfunction
Visual EPs (cortical latencies)
1) Optic nerve, hypothalamic, pituitary gland, and diaphragma sellae surgery
2) Post-anoxic comatose patients (prognosis dimension—outcome prediction)
3) Hypothermic comatose patients (prognosis dimension—outcome prediction)

***EMG*:** electromyogram; ***EEG*:** electroencephalogram; ***QEEG*:** quantitative electroencephalogram.

changes may occur before the usual cerebral physiological or pathophysiological changes [82] allowing earlier therapeutic adjustments. Some illustrative examples of successful MCD-motivated insulin therapy modifications have been published with the opportunity to determine individual optimal glycaemia threshold [80]-[85]. More and more often combined with the brain tissue oxygen tension (PbtO2), cerebral MCD is also able to optimise the Mean Arterial Pressure (MAP)/Cerebral Perfusion Pressure (CPP) [86] [87] and the transfusion thresholds [88] in patients at high risk of secondary brain ischaemia [89]. This has led to the establishment of guidelines in comatose patients for various problems [90] [91]. Moreover, a correlation has been demonstrated between variations in early biological markers and long-term outcome [92] supporting the concept of a possible influence of brain energy modulation on patient outcome. Despite these exciting results, MCD technology has an intrinsic limitation: the analysis is limited to the area surrounding the catheter tip, making this monitoring only local or even regional (**Table 2**). To bypass this problem, some successful experiences of multicatheter insertion have been reported, confirming the quality of the information provided by MCD, unfortunately too limited for now [93].

9. Brain Oxygen Monitoring

9.1. Jugular Venous Oxygen Saturation (SjvO2)

In this category of CNS monitoring, SjvO2 is the oldest since it was proposed in clinical practice from the 1940s. After a resurgence at the beginning of the 1990s, sustained by the availability of fibreoptic oximetric catheters, there has been a progressive lack of interest, which is related to the intrinsic weaknesses of this parameter and the concomitant emergence of new competitive technologies (see below). The difficulty of keeping the tip of the catheter in a good place (despite some attempts of ultrasound-guided optimisation, which was unfortunately not generalised), with the correlated high risk of displacement, particularly in awake but non-cooperative patients [94] [95]; the possibility of extracranial blood contamination; the lack of sensibility and specificity to detect limited brain ischaemia have often made the rational interpretation of SjvO2 too difficult and non-pertinen [96]. This is why, nowadays, SjvO2 is progressively competed by newer technologies.

9.2. Brain Tissue Oxygen Tension

The brain oxygen supply depends on cerebral blood flow (CBF), and the partial pressure of oxygen in brain tissue or brain oxygen (PbtO2 = product of CBF and cerebral arteriovenous oxygen tension difference) represents an effective indicator that is, nevertheless, more indicative of oxygen diffusion than cerebral metabolism [97]. PbtO2 is measured on-line via specific probes inserted in subcortical white matter, through multiple-lumen bolts adjacent to ICP monitors, but can also be measured in penumbral tissue, such as around haemorrhagic contusions or in areas at risk for secondary delayed vasospasm/ischaemia. Furthermore, PbtO2 is additional to ICP monitoring in guiding the management of CPP [98]. The response of PbtO2 to CPP/MAP increase allows the tailoring of the individual CPP threshold [98] [99]. Combined with TCD and neuroimaging, PbtO2 reactivity is adapted to manage delayed cerebral ischaemia in comatose patients with subarachnoid hemorrhage (SAH) when the classical influence factors are SaO2, ScO2, PvO2, and haemoglobinaemia, and while moderate hyperventilation [100], protective ventilation [101], and blood transfusion [102] may even be adjusted using PbtO2. Regarding neuro-trauma, a low PbtO2 without reactivity is a strong marker of poor outcome [103] and a discordant low PbtO2 may occur while ICP and CPP remain within the recommended thresholds [104]. This high intrinsic value has led to the recent incorporation of this topographical parameter into the recommendations for the brain injured patient [105] [106]. The progressive multiple parameter adjustment to increase PbtO2 has even been proposed as a useful way to identify “PbtO2 responders” with a better outcome [107]. However, despite this positive trend, the real impact on patient outcome of PbtO2-directed therapy remains controversial [105] [106] [108] and needs further investigations to clarify the vision. Nevertheless, the clinical relevance, safety, and effective documentation in the literature make the PbtO2 a quite systematically recommended parameter in routine CNS multimodal monitoring.

9.3. Cerebral Oximetry (SctO2) Using Near-Infrared Spectrometry (NIRS)

The measurement of SctO2 using NIRS technology [109]-[111] represents a newer alternative to PtbO2 for the direct measurement of cerebral tissue oxygenation. Different methodologies exist and are commercially availa-

ble [112]: modified Beer-Lambert law, multidistance or spatially resolved spectroscopy, frequency-resolved (domain) spectroscopy, and time-resolved spectroscopy. Before being used for cerebral oximetry monitoring in anesthesia and in intensive care, NIRS was developed by neuroscientists and neurocognitivists for brain function investigation [113] [114]. Briefly, a rapid change in NIRS, recorded spontaneously or after stimulation, is directly correlated to the variation of function of the neural tissue just below the electrode, based on the "near-infrared window" concept [115] and the event-related evoked optical stimulation (EROS), a suitable and attractive method for the cognitive neurosciences [116].

In this context, NIRS has been topographically used in fundamental research, using relatively complex multiple electrode montages over the skull [117], corresponding to a new category of functional brain mapping, alone or combined with EEG [118], showing the complementarity of these technologies. Alternatively, for the intraoperative period or in the ICU, different dual-channel oximeters simplified for clinical practice (FORE-SIGHT device, CAS-Medical Systems, Brandford, CT, USA; INVOS series, Somanetics, Troy, MI, USA; and NIRO series, Hamamatsu Photonics K.K., Hamamatsu City, Japan) may be used.

Two electrodes disposed on the forehead of the patient would give information about oxygenation in the right and left cerebral hemispheres. Basically, NIR cerebral oximetry does not rely on pulsatile flow but measures a weighted average of arterial, capillary, and venous compartments (unfortunately, by cumulative assessment) in proportion to their relative intracranial volumes within the field of view [119]. It is measured following different physical methods (regional cerebral saturation by the INVOS series, tissue oxygenation index by the NIRO series, and SctO2 by the FORE-SIGHT device), making sometimes difficult the comparison. For instance, despite normative values of SctO2 of between 60% and 75% and a coefficient of variation for absolute baseline values of approximately 10% [120] being validated for the healthy brain, a wide intra- and inter-individual baseline variability remains a potential problem. The use of NIRS to guide the manipulation of systemic physiology to minimise the risk of cerebral hypoxia/ischaemia during carotid endarteriectomy (CEA) is an area where NIRS needs to be proved to have at least equivalent sensitivity and specificity to the other recommended modalities of monitoring [121]-[123]. NIRS has not been clearly proven to be superior for identifying critical cerebral ischaemia. The body of evidence suggests only a broad equivalence to other modalities, albeit with uncertainty as to the exact NIRS-derived threshold for the identification of critical ischaemia [124]-[126] (low positive predictive value). Regarding cardiac surgery, the absence of compelling data to support the use of NIRS-guided management strategies to reduce the incidence of postoperative cognitive dysfunction and stroke has not prevented NIRS from gaining popularity as a monitoring modality for the management of cerebral oxygenation during cardiac surgery [127] [128], particularly taking in account the significant associated over-cost (electrodes).

However, a recent review suggests that the neurocognitive decline after cardiac bypass surgery may not only be related to the intervention but may also reflect the natural decline of patients with multiple comorbidities raises an important question about the impact and value of neuro-monitoring, including NIRS, to guide treatment during cardiopulmonary bypass [129]. Otherwise, NIRS has been suggested for monitoring the healthy but at-risk brain during routine surgical procedures under general anesthesia, but always without real confirmation [130]. In this context, patients undergoing surgery in the beach chair position could take advantage of SctO2 monitoring. Severe hypotension occurs in up to 20% of patients [131] and ischaemia-related cerebrovascular events have been reported [132]. It was first reported in an isolated case [133] [134] and then demonstrated by an observational study [135] of shoulder arthroscopy in a beach chair versus lateral decubitus position and using a FORE-SIGHT™ oximeter, which demonstrated cerebral desaturation in 80% of patients in the beach chair position compared with none in the lateral decubitus position. Nevertheless, there was no postoperative neurological impact, only a higher incidence of nausea and vomiting, supporting the hypothesis that brain oxygenation might be a surrogate of the adequacy of non-neurological organ perfusion.

Regarding brain injury in the ICU, the complex relationships between NIRS and other physiological variables (ICP, blood flow velocity, etc.) routinely used to assess cerebrovascular reactivity make it necessary to apply more complex analytical techniques to perform qualitative and quantitative analysis of cerebrovascular reactivity that is not available with other methods [136]. This way, NIRS might potentially provide the monitoring of cerebral autoregulation, although this is uncertain at present. However, compared with PbtO2, NIRS lacks power for brain ischaemia detection in neuro-ICU [137]. For now, PbtO2 remains the method of choice, but SctO2 by NIRS is not necessarily inferior. The problem is trying to define the real interest and indications of this user-friendly, noninvasive monitoring modality. With several practical advantages in comparison to other neuro-

monitoring techniques (invasive or minimally invasive), such as the capability to make measurements over multiple regions of interest simultaneously with high temporal resolution, NIRS might potentially monitor regional cerebral oxygenation, haemodynamics, and metabolism, and could guide therapeutic brain protection strategies. For now, mainly validated when ischemia occurs in normal and healthy brain monitoring without major neurological problem, it seems to suffer from a lack of concrete recommendations for use, bearing in mind that NIRS technology has the potential benefit of multiple recording sites either at the skull level (brain mapping similar to EEG and QEEG) or at extracranial sites for muscular oxygenation and metabolism follow-up [138] [139] or peripheral perfusion [140] [141].

To summarise (**Table 7**) regarding the three methodological options for brain oxygen monitoring, the maximal interest in SjVO2 was shown 10 to 15 years ago. It has been progressively replaced by the minimally invasive PbtO2 monitoring that is now more and more well established in clinical practice, while SctO2 by NIRS has not found its proper place in clinical practice in relation to its intrinsic practical advantages, and truly needs a clearer and objective definition of its recommended uses.

Table 7. The three methodological options regarding cerebral brain oxygen monitoring.

	Jugular venous oxygen saturation (SjvO2)	**Brain tissue oxygen tension (PbtO2)**	**Cerebral oximetry using near-infrared spectrometry (SctO2 – NIRS)**
Basic principle -indicator	Oxygen consumption —oxygen need—cerebral metabolism	Oxygen diffusion > cerebral metabolism	Oxygen consumption—oxygen need—cerebral metabolism in normal healthy brain
Applicability	Continuous at bedside	Continuous at bedside	Continuous at bedside
Application fields	Intraoperative ICU	Intraoperative ICU	Intraoperative ICU
Device	Invasive	Minimally invasive	Non-invasive (main advantage)
Limitations of use	-Catheter tip displacement -Compiled hemispheric measurement -Lack of detection of limited ischaemia -Extracranial blood pollution	-Local or regional measurement -Site-dependent measurement	-Mainly healthy brain monitoring -Inter- & intra-individual variability -Complex multi-factor brain pathophysiological process -Compiled hemispheric measurement -Desaturation ≠ real ischaemia and infarction -Specific SctO2 determination methodology of each device
Cost-investment	-Monitoring -Probe (reusable or single use)	-Monitoring -Probe (single use)	-Monitoring -Probe (single use)
Technical expertise, management & nursing	Advanced Time-consuming	Advanced Time-consuming	Basic (intuitive)
Specific infrastructure for insertion	Special need (invasive, ICU, or OR)	Special need (minimally invasive, OR)	No need
Ischaemia detection	Hemispheric (focal ischaemia undetected)	Local (insertion site-dependent)	Hemispheric
CPP correlation		CPP < 60 mmHg: PbtO2↓ CPP > 60 mmHg: PbtO2 ≈ or ↑	Variable (+/− more specific than SjvO2)
Numeric values	-Normal: 60% - 90% -Critical: 50% - 55% during 15 min = cerebral ischaemia	-Normal: 25 - 35 mmHg -Critical: <15 mmHg = ischaemia -<6 mmHg = infarction, even cerebral death	-Normal: 60% - 75% -Baseline variation: 10% -↓13%: ischaemic threshold -35% during 2 - 3 h: infarction
Thresholds correspondance	50%	8.5 mmHg	To be determined-variable (correct for internal carotid clamping, circulatory arrest)

***ICU*:** intensive care unit; ***OR*:** operating room; ***CPP*:** cerebral perfusion pressure.

10. Cerebral Blood Perfusion

10.1. Regional Cerebral Blood Flow

PbtO2 (for the physiological definition, see the "Brain tissue oxygen tension" section) represents only an indirect assessment of the CBF influenced by external factors [98]. A recent technological alternative allows the direct measurement of regional blood flow (rCBF) via a thermal diffusion probe (TDP; Hemedex, Cambridge, Massachusetts, USA), giving results in absolute units. This probe may be inserted into the brain parenchyma, close to the ICP/PbtO2 probes (cf. multimodality concept). It can be either tunnelled from the surgical area or directly bolted (stable fixation of the probe through a skull bolt to avoid catheter dislodgement). Similar to PbtO2, the probe tip provides a quantitative measurement only in the spherical volume of tissue surrounding the sensor. The TDP technology was first successfully validated by comparing the rCBF measurements with the xenonCT [142]. Insertion of the probe 2.5 cm below the dura in the white matter is checked using a CTscan. Otherwise, for the rCBF assessment, the TDP remains dependent on a stable patient temperature trend. Severe hyperthermia and the patient's temperature instability significantly affect the rCBF numerical value.

In brain injured patients (subarachnoid haemorrhage, trauma, etc.), the TDP combined withPbtO2 seems very relevant for optimising CPP management [143] [144]. The results suggest that rCBF-guided MAP/CPP increase could efficiently replace the classical "triple-H" therapy. The main problem remains to define the most judicious site of insertion of the electrode [145]-[147]. Placed at a good site, rCBF allows the assessment of cerebrovascular reactivity to PaCO2 variations, which is greatly useful for driving moderate hyperventilation, particularly in patients with at least partially altered cerebral autoregulation [148] [149].

Less advanced than PbtO2 technology in its systematic integration into multimodal neuro-monitoring, rCBF could progressively take a part after, of course, the confirmation of its validity and its implementation in a large population of neurological patients.

10.2. Local CBF

For the continuous measurement of CBF at the patient's bedside, Laser Doppler Flowmetry (LDF)represents an old but efficient alternative. The Oxylab LDF system(Oxford Optronix, Abingdon, UK) measures red blood cell movements within the microcirculation only 1cm below the dural surface [150] [151], using several possible local devices (surface angular, needle and micro-needle, and endoscope). The physical principle is to invest a smallvolume of cerebral matter (limited to the cortex), but with the highest possible spatial resolution. This is why the LDF does not qualify as regional CBF monitoring but only as local CBF monitoring and is, till now, mainly used in laboratories for fundamental neuro-investigations in small animals (rats, gerbils, rabbits, or cats), for which it is currently a sort of gold standard. However, the LDF has been investigated for use in neurosurgery for a long time, with satisfactory results regarding the early detection of ischaemia and treatment guidance and adjustment [152]-[155], but a possible significant and beneficial impact on patient outcome was never proved. On the other hand, some authors have considered the mapped multi-insertion of LDF probes as a solution to the problem of the limited volume of investigated cerebral matter, at the main condition to select as judiciously as possible the different probe insertion sites. However, this has never been reported in clinical practice. On the other hand, the LDF has been proved to monitor efficiently local spinal cord blood flow in one animal model [156]. Unfortunately, no consistent comparative data have been published on local CBF monitoring using LDF and rCBF, followed up with TDP. However, in a recent article, LDF seems to be logically more sensitive than TCD in detecting cortical autoregulation disturbance during rising ICP and falling CPP in the area of distribution of the middle cerebral artery [157]. This lack of clinical results makes it quite impossible to have a definitive overview and is a little frustrating.

10.3. TCD, Microvascular Doppler, and Cerebral Tissue Doppler

Today, TCD is a full element of CNS monitoring despite its limited metabolic and functional dimension, being completely indirect. With the constant and even growing interest in this technology, it is regularly upgraded [158]. In fact, except rCBF and local CBF monitoring, TCD provides the only Foods and Drugs Administration-cleared method to continuously and directly monitor change in cerebral haemodynamics, mainly in perioperative and critical care settings, to give clinically valuable and potentially life-saving information [159] [160]. The technology evolution gives the operator the opportunity of more and more substantial morphological infor-

mation's [161] about the cerebral vasculature. However, the quality of this monitoring is heavily influenced by the training, skill, experience, and practice of the sonographer. Beside TCD, microvascular Doppler ultrasonography [162] is the only dedicated intraoperative to the check of vascular neurosurgery (aneurysm clipping, vascular bypass of giant aneurysm or arteriovenous malformation, etc.) as a potentially powerful alternative to fluorescein angiography, since the Doppler technology is able to give not only qualitative but also quantitative information. Additionally, it is increasing thought that Doppler technology can be used not only to monitor cerebral vessels but also brain parenchyma, where it would probably be very informative about CBF in a less limited area than the two other methods.

To summarise regarding CBF monitoring methods (**Table 8**), TCD has advantages with possible evolutions and improvements, may be completed by the assessment of tissue blood flow by Doppler. This sort of a multimodal Doppler tool could be very valuable and powerful. In the meantime, the more limited (local or regional) methods of monitoring of CBF remain of interest, but what can be done with them and for which types of patients have not been clearly defined.

11. Conclusions

To conclude, I would like to first list some key learning points that form the foundation of efficient neuromonitoring:

Table 8. The three methodological options regarding cerebral blood flow (CBF) monitoring.

	Regional CBF (rCBF) Thermal Diffusion Probe (TDP)	Local CBF (lCBF) Laser Doppler Flowmetry (LDF)	Transcranial Doppler (TCD)
Basic principle -indicator	Thermal diffusion in a spherical volume around the tip of the probe	Red blood cell movement within the microcirculation beside the probe	Major vascular Doppler effect coupled with two-dimensional ultrasonography
Applicability	Continuous at bedside	Continuous at bedside	Continuous at bedside
Application fields	Intraoperative (to be developed) ICU	Intraoperative (to be re-evaluated and developed) ICU	Intraoperative ICU
Device	Minimally invasive (2 - 2.5 cm below the dura)	Minimally invasive (1cm below the dura)	Non-invasive (main advantage)
Limitations of use	-Measurement and monitoring of rCBF only in the spherical area (1 - 1.5 cm diameter) around the probe tip -Site-dependent measurement	-Measurement and monitoring of lCBF only in the 1 or 2 mm surrounding the probe tip -Site-dependent measurement	-Arterial CBF in medium size vessels (MCA > ACA > PCA) -Not tissue monitoring -Possible instability of the probe
Cost-investment	-Monitoring -Probe (single use)	-Monitoring -Probe (single use)	-Monitoring -Probe (reusable) -Fixation system for probes
Technical expertise, management & nursing	Basic Time-consuming	Basic Time-consuming	Advanced
Specific infrastructure for insertion	Special need (minimally invasive, ICU, or OR) Probe tunneled or bolted	Special need (minimal invasive, ICU or OR) Probe tunnelled or bolted	No need
Ischaemia detection	Local or regional Cortical and subcortical (following the insertion's adequacy)	Local Cortical (following the insertion's adequacy)	Hemispheric or global
CPP correlation	Vasoreactivity and autoregulation	Vasoreactivity and autoregulation	Variable Vasoreactivity and autoregulation
Numeric values	-Normal: 40 - 70 $mL \cdot 100^{-1} \cdot min^{-1}$	-Normal: 80 $mL \cdot 100^{-1} \cdot min^{-1}$ (temporo-sylvian cortex) and 60 - 65 $mL \cdot 100^{-1} \cdot min^{-1}$ (fronto-latero-dorsal cortex)	-Normal: 30 - 80 $mL \cdot 100^{-1} \cdot min^{-1}$ Following the artery and based on the velocity assessment

***MCA*:** middle cerebral artery; ***ACA*:** anterior cerebral artery; ***PCA*:** posterior cerebral artery; ***ICU*:** intensive care unit; ***OR*:** operating room; ***CPP*:** cerebral perfusion pressure.

Table 9. Proposal about the potential multimodal combinations of neuro-parameters of advanced neuro-monitoring in the near future for the intraoperative and/or intensive care unit settings (based on the scientific literature reflecting the actual worldwide practice and on my own practice). For each clinical situation, two to three technologies can be combined. Dark grey indicates validated usual and recommended elements of monitoring. Medium grey indicates parameters with a high level of evidence (equivalent to a recommendation or quite equivalent) In this case; there is consistent scientific literature to support making these parameters probably recommended in the next years. Light grey indicates parameters that require clinical investigations to try to define or to refine the real value. For these, clinical recommendations remain unclear and only potential. Very light grey (regional cerebral blood flow [rCBF] column) is just to point out that rCBF by TDP could be an alternative (or a second choice) to lCBF by LDF that is preferred because of the smallness of the probe.

	EEG‡	EP	MCD	SvjO2	PbtO2	SctO2 (NIRS)	rCBF (TDP)	lCBF (LDF)	TCD
Intraoperative neuromonitoring									
1. Neurosurgery									
Invasive spine or spinal cord surgery		SEP/MEP							
Deep or intermediate hypothermia for brain vascular neurosurgery		SEP/VEP AEP							
Normothermic brain vascular neurosurgery		SEP/VEP AEP							
Cortical brain tumour resection (meningioma and astrocytoma)									
Posterior fossa surgery*		SEP/AEP							
Epilepsy surgery**									
Awake surgery***									
Optic nerve, hypothalamic, pituitary gland, and diaphragma sellae surgery****		VEP							
Surgical peripheral nerve release		SEP/MEP							
2. Cardiac & vascular surgery									
Normothermic thoracic and thoracoabdominal aortic surgery		SEP/MEP							
Normothermic cardiac or vascular surgery									
Intermediate hypothermia for cardiac or vascular surgery		SEP/VEP							
Deep hypothermia for cardiac or vascular surgery§		SEP/VEP							
Carotid endarterectomy		SEP/VEP							
Intensive care unit									
Post-anoxic coma		SEP/VEP SEP/AEP							
Hypothermic coma		SEP/VEP SEP/AEP							
Intoxication and poisoning		SEP/VEP SEP/AEP							
Brain death		SEP/VEP SEP/AEP							
Non-epileptic seizures		SEP/VEP							
Status epilepticus		SEP/VEP							
Subarachnoid haemorrhage		SEP/VEP SEP/AEP							
Stroke (acute phase)		SEP/VEP SEP/AEP							
Trauma brain injury		SEP/VEP SEP/AEP							
Trauma spinal cord injury		SEP/MEP							

‡including quantitative EEG (QEEG) but not necessarily simplified forehead EEG-derived technologies; *including intra- and extracranial surgery of the auditory and/or facial nerves; **including surgical lobectomies and other resections, electrocorticography and stereo-EEG electrodes insertion, and intraoperative cortical stimulation; ***including fully awake procedures and asleep-awake-asleep procedures; ****including open and/or endonasal approaches; §including therapeutic and deliberate cardiac arrest; ***rCBF*:** regional cerebral blood flow; ***TDP*:** thermal diffusion probe; ***lCBF*:** local cerebral blood flow; ***LDF*:** laser Doppler flowmetry; ***EEG*:** electroencephalogram; ***EP*:** evoked potentials; ***MCD*:** microdialysis; ***SvjO2*:** jugular venous oxygen saturation; ***PbtO2*:** brain tissue oxygen tension; ***SctO2*:** Cerebral oximetry using near infrared spectrometry; ***TCD*:** transcranial Doppler.

1) The variability of CNS metabolism and function is typical of the different anesthetic phases and in comatose patients. Influenced by physiological and pathophysiological factors, one of our main challenges is to impact it as efficiently as possible.

2) Regarding CNS metabolism and function monitoring, a minimal subdivision has to be respected: the cerebral cortex and deeper structures as interdependent entities, each with a high level of differentiation and complexity.

3) The different cerebral cortical areas are dedicated to different functions and their pharmacological and pathophysiological sensitivity is not similar orhomogeneous. This underlies the concept of topographical investigations for mapping.

4) Regarding not only the electrical signals of the CNS but also the other specialized neuro-monitoring modalities, they potentially have dual dimensions: basic spontaneous activities and advanced evoked responses.

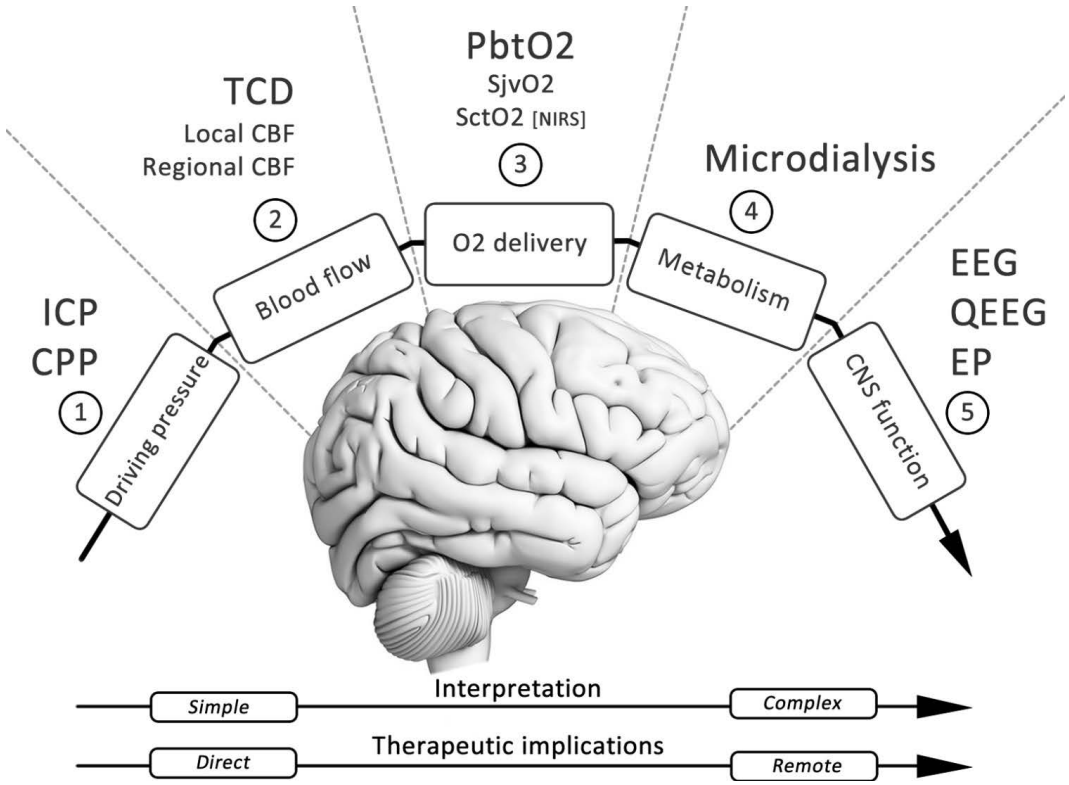

Figure 1. Do we need a more advanced brain and spinal cord monitoring to follow metabolism and function? To make more concrete the multimodal approach, it is possible to put in accordance the different possible modalities of CNS monitoring to the respective level in the phenomenological chain leading to the highest complexity: the CNS function and neurons functioning, on right. First, the driving pressure method is based on the usual and continuous monitoring of the ICP and CPP. Second, about CBF assessment, the TCD remains the reference technique even if local CBF (lCBF) or regional CBF (rCBF) would deserve to be considered a new time. Third, to follow the 02 delivery, the PbtO2 has progressively supplanted the classical SjvO2, without to be really competed with the cerebral oximetry, remaining an O2 cerebral diffusion indicator rather than a really metabolic parameter. Fourth, the metabolism is essentially related by the microdialysis technique for which an increased glutamate, a high lactate/pyruvate ratio with a low glucose in the brain relate a CNS cellular hypoxia. Finally, in point 5, the electrophysiology is alone able to give an idea of the CNS function and neurons functioning. About the phenomenological chain from point 1 to point 5, each item is required for the further factors downstream as in a sort of cascade. The corresponding monitoring items progress from the most basic (on left) with the simplest interpretation to the most advanced (on right) with more complex results sometime difficult to put in perspective with the patient situation. Similarly, the impact on the patients' treatment varies from direct to remote or indirect. However, the level of the accuracy of the information's given by the successive monitoring's is progressively growing up, counterbalancing the apparent awkwardness of use. The investment of time to know how to use the different modalities of this monitoring would be always very productive and beneficial either for the clinicians or particularly for the patients.

5) Multimodality, which is more and more recommended in practice, has to try to define the most judicious combination of parameters from different origins (electrical, oxygen consumption and supply, and blood perfusion and supply) to give the best possible answer for the specific patient's situation.

6) Electrophysiology (EEG, QEEG, and evoked potentials) represents a cornerstone but remains underused because of the absolute need for education.

7) Regarding brain oxygen monitoring, PbtO2 has now supplanted SjvO2 and represents the reference technology. As for SctO2 by NIRS, it is still controversial and we have to wait some more years for definite and strict recommendations for use.

8) Regarding cerebral perfusion, rCBF is interesting but is, unfortunately, too site-dependent to be sufficient. LDF has to be re-evaluated in clinical practice to refine its real interest, specificity and sensitivity. This is the only one with a specific potential interest about spinal cord blood flow monitoring owing to the smallness of its probe.

Finally, regarding brain and spinal cord metabolism and function, continual developments in monitoring methods provide more and more valuable information and more and more accurate answers to questions about potential problems. As to what is called "multimodality" and within the available technologies listed in this article, someone's, older, are more investigated and evaluated in clinical practice and others, more recent are still waiting to find their respective position in the neuro-monitoring arsenal. Far from excluding any technology, the best remains to learn and to know as much as possible what they are and what we can expect of them, to limit the risk of misuse and misevaluation. The development of a real effective neuro-monitoring, combining one monitoring modality of each family (electrophysiology, microdialysis, brain oxygen, and CBF) could be the final solution (**Table 9**). To make more concrete this sort of methodic approach, it is also possible to classify the different modalities according the level in the phenomenological chain leading to the highest step of complexity: the brain or spinal cord function (**Figure 1**). For now, this idea remains only conceptual but this is our role for the next years, to drive investigations to have the opportunity to justify the usefulness of this second generation neuro-monitoring.

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