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REVIEW ARTICLE

Brain health

A concern for anaesthesiologists and intensivists

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Damage to the brain can have disastrous and long-lasting consequences. The European Society of Anaesthesiology and Intensive Care (ESAIC) is aware of the importance of taking good care of the brain, both of patients and of anaesthesia and intensive care unit (ICU) caregivers, and has organised a complete learning track on brain health to bring this concern to the attention of practitioners. This learning track included an online Focus Meeting on Brain

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Health (November 25, 2023). We here provide readers with a digest of the information that was delivered during that meeting in an opinion paper driven by the authors' own reading of the literature. It is divided according to the meeting's sessions, including how to improve the health of an injured brain, how to keep a young or old brain healthy, how to keep a healthy adult brain unimpaired, how monitoring can impact brain health in the operating room and in the intensive care unit, and how to keep the anaesthesia and ICU caregivers' brain healthy. Each part is a brief and focused summary. The main delivered messages are that the management of injured brain patients involves an adequate choice of sedation, adequate brain monitoring, and focused attention to specific points depending on the underlying pathology; that several measures can be undertaken to protect the brain of the very young needing anaesthesia; that it is possible to detect older patients at risk of postoperative neurocognitive disorders, and that dedicated perioperative management by a multidisciplinary expert team may improve their outcomes; that apparently healthy adult brains may suffer during anaesthesia; that the electroencephalogram may track peri-operative brain dysfunction, and that female patients should be given special care in this respect; that multimodal brain monitoring helps to detect pathological processes and to maintain brain homeostasis; and that burnout in anaesthesiologists can be effectively fought using personal, organisational, managerial and legal approaches.

Introduction

Brain health, surely, is an essential goal for anaesthesiologists and intensivists. The brains of patients are submitted to stressors not only during the perioperative period, but also in the intensive care unit (ICU). The brain is the primary target of anaesthesia and sedation, which may not have only beneficial effects, particularly if the organ must respond to the insult of surgery or critical illness at the same time. The sensitivity of the brain to stressors may vary according to patient-specific factors, including age, sex, comorbidities, and preexisting brain injury. Aside from patients, anaesthesiologists, and particularly trainees, are sometimes confronted with intense psychological pressure, due to the work environment and the high level of responsibilities related to our profession. This may impact on their brain health, and, secondarily, on the quality of patient care. The European Society of Anaesthesiology and Intensive Care (ESAIC) and its Scientific Committee are aware of the importance of taking care of the brain, both for patients and for anaesthesia and ICU caregivers. To bring this concern to the attention of the anaesthesiology and intensive care community, the ESAIC has decided to schedule a complete learning track on brain health. This started in October 2023 with four 'Theme of the Month' webinars, followed by an online Focus Meeting on brain health on 25 November 2023, a podcast of the Focus Meeting key learning points released on 26 December 2023, and a 'TryMe! Quiz' accessible online during the whole year. This learning track concluded at the Euroanaesthesia meeting, held in Munich from 25 to 27 May 2024, with hands-on workshops and specific panel discussions.

The purpose of this follow-up article is to provide readers with a digest of the information that was delivered during the November Focus Meeting by experts in anaesthesiology, intensive care medicine, critical emergency medicine and neurology. It must be seen as an opinion paper driven by the authors' own interpretation of the literature. It can be considered as a current opinion of the anaesthesiology and intensive care community on brain health, taken in a broad sense. It will be divided according to the sessions that were proposed during the above-mentioned meeting, which attempted to address the questions on how to improve the health of an injured brain, how to keep a young or old brain healthy, how to keep a healthy adult brain unimpaired, how monitoring can impact brain health in the operating room and in the ICU, and how to keep the anaesthesia and ICU caregivers' brain healthy. Each part is a brief and focused summary, aiming at helping practitioners to adequately manage patients in the above-listed situations, and probably at helping them to manage their own brain. A figure for each part is designed as a graphical abstract, to summarise the main learning points. Throughout the manuscript, information corresponding to current clinical knowledge will appear in italics, to help the reader distinguishing between this type of information and other elements that should be considered, although not benefiting from strong evidence.

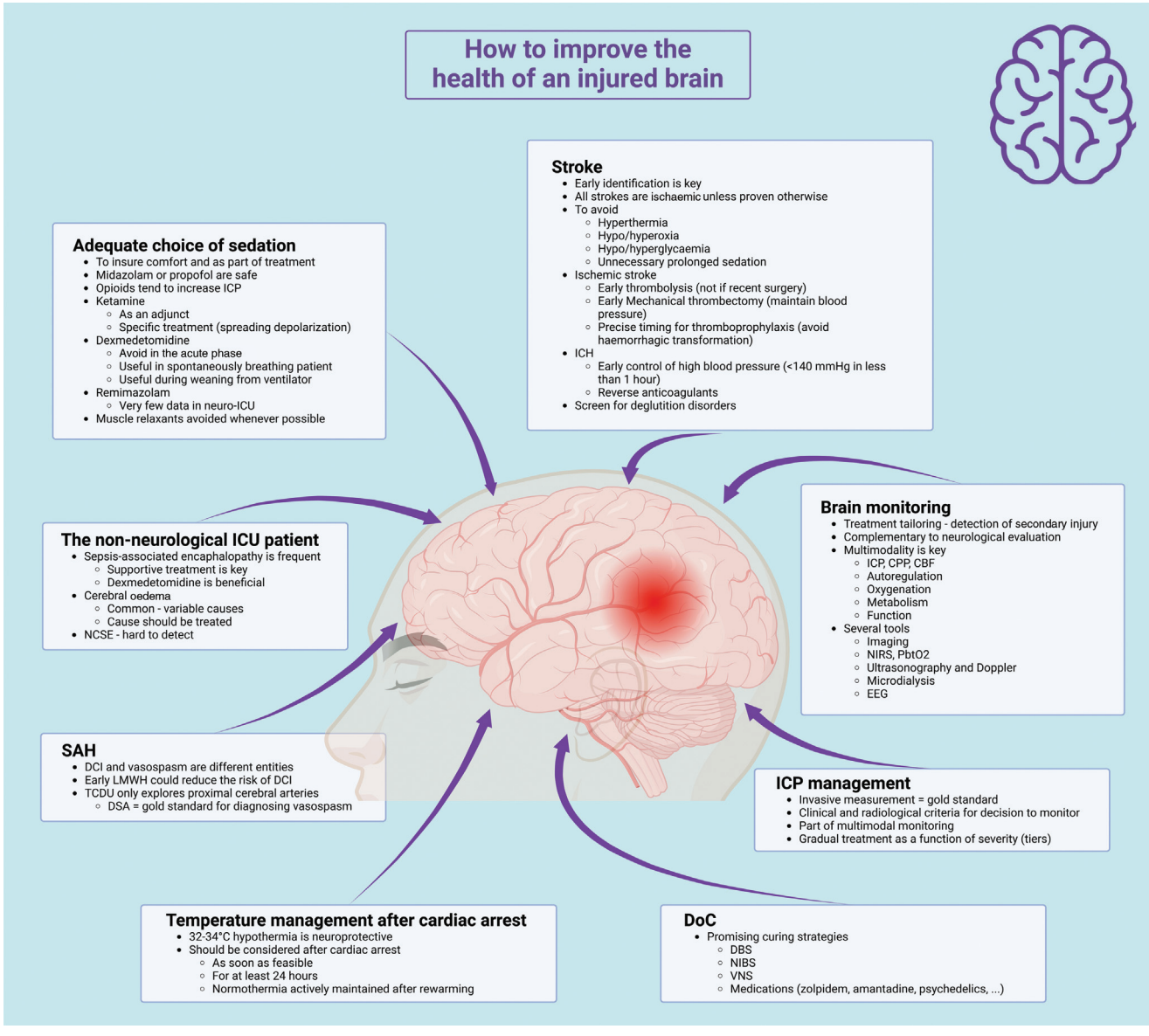
How to improve the health of an injured brain

A graphical abstract of the key points delivered in this part is provided in Fig. 1.

Brain monitoring in the intensive care

Acute brain injury patients such as those with stroke or trauma, or with a brain injury after cardiac arrest are at an increased risk of secondary brain injury, which, unlike the primary brain injury, is preventable and treatable. Brain monitoring can help detecting early neurological worsening due to secondary brain injury before irreversible brain damage occurs, and can guide individualised patient management.[1] Brain monitoring can also help assessing the response to treatment and identify possible adverse effects. It provides a better understanding of the complex pathophysiology of different types of acute brain injuries, and can help designing and implementing management

Fig. 1 How to improve the health of an injured brain.



CBF, cerebral blood flow; CPP, cerebral perfusion pressure; DBS, deep brain stimulation; DCI, delayed cerebral ischaemia; DSA, digital subtraction angiography; EEG, electroencephalogram; ICH, intracerebral haemorrhage; ICP, intracranial pressure; ICU, intensive care unit; LMWH, low-molecular-weight heparin; neuro-ICU, neurological intensive care unit; NIBS, noninvasive brain stimulation; NIRS, near infrared spectroscopy; $PbtO_2$, brain tissue partial pressure in oxygen; SAH, subarachnoid haemorrhage; TCDU, transcranial Doppler ultrasonography; VNS, vagal nerve stimulation.

protocols aiming at improving neurological outcome and quality of life in survivors.[1] Importantly, current opinion promotes the use of a multimodal approach for brain monitoring. It should consist of a combination of invasive and noninvasive assessments, integrating neurological examination, imaging, as well as the physiological and electrical assessment of brain function.

Clinical neurological examination is the cornerstone of neuromonitoring and should be routinely performed. Neurological examination allows the timely detection of neurological changes, indicating the need for an intervention to reduce the extent of secondary brain injury. It also helps localising the injury, determining its focal, global, peripheral or central nature, which can guide further diagnostic testing and treatment. *Clinical examination can also have a prognostic value.*[2] However, a complete clinical assessment is not always possible insofar as, frequently, acute brain injury patients have impaired consciousness, are mechanically ventilated, and receive sedation.[3] Integrating different techniques and modalities of monitoring allows a comprehensive assessment of

brain structural integrity (imaging) and function including cerebral haemodynamics, oxygenation, metabolism and electrophysiology.[1]

Imaging encompasses classical radiological techniques such as computed tomography (CT) and MRI. Such imaging is mandatory in the management and monitoring of acute brain injury patients.[3] Imaging should be performed upon admission, after interventional procedures or neurosurgical interventions, and at the onset of a neurological deterioration, to assess the evolution of injury and the occurrence of complications. Brain imaging localises the injury, provides information on the extent of structural damage and salvageable tissue and has prognostic implications. Some CT or MRI modalities offer the possibility to look at the brain circulation, providing information on vessel anatomy and the perfusion status of the brain. Brain imaging also helps select the appropriate location to place invasive neuromonitoring devices and checking their correct placement. The interest in imaging techniques by brain ultrasonography for brain-injured patients is currently growing, as it is a well tolerated and noninvasive, allowing a reliable assessment of brain anatomy and the detection of lesions. For example, colour-duplex sonography is useful for detecting a midline shift,[4] which is an important sign of severely raised intracranial pressure (ICP), and circulatory arrest.[5]

Looking at the underlying brain physiology and its alterations is possible through several modalities. Cerebral blood flow (CBF) absolute value can be measured noninvasively using neuroimaging techniques such as xenon-enhanced CT, PET and perfusion CT,[6] but these are not applicable at the bedside and necessitate the transport of the patient. An invasive method, the intraparenchymal thermal diffusion flowmetry, allows a direct measure of regional CBF with a high temporal resolution.[7] Transcranial Doppler, another modality of brain ultrasonography (TCDU), permits an indirect assessment of CBF, through the measurement of velocities in cerebral arteries. Other parameters of interest are ICP and cerebral perfusion pressure (CPP). Maintaining adequate perfusion is essential for brain function. Intracranial hypertension is known to be associated with poor outcomes after an acute brain injury. In this context, invasive ICP and CPP monitoring are often recommended. An ICP above 20 to 22 mmHg usually indicates the need for treatment,[8] even if the evidence regarding the effect of ICP monitoring on patient outcome improvement is poor.[1] The most common techniques for measuring ICP are invasive and involve an intraparenchymal probe or an intraventricular catheter. Intraventricular catheters can be calibrated whenever needed and may be preferred in patients with intraventricular haemorrhage and those at risk of hydrocephalus as it allows cerebrospinal fluid (CSF) drainage. However, *intraventricular catheters are associated with a higher risk of infection as compared with intraparenchymal probes*. CPP is taken as the difference between mean arterial pressure (MAP) and ICP. Noninvasive techniques exist to estimate ICP and CPP. For example, ultrasonography of the eye permits the measurement of the optic nerve sheath diameter (ONSD), which is a surrogate measure of raised ICP. This can also be done on a brain CT.[9] TCDU can provide ICP estimations from the measurement of CBF velocity in the middle cerebral artery (MCA) and the associated pulsatility index,[10] and can detect vasospasm of those arteries. Regional cerebral oxygenation can be assessed noninvasively using near-infrared spectroscopy (NIRS), which measures mean regional arteriovenous oxygen saturation (rSO_2) using wavelength-dependent light attenuation. This measurement is susceptible to extracranial contamination and should rather be used to assess the trend of rSO_2 over time than its absolute value.[11] More invasive techniques for assessing brain oxygenation are the brain tissue partial pressure in oxygen ($PbtO_2$) monitoring and the jugular bulb venous oxygen saturation ($SjvO_2$) monitoring. Currently, $PbtO_2$ is the preferred method. It reflects the balance between oxygen delivery and oxygen consumption. Oxygen delivery depends on CBF, haemoglobin concentration and arterial oxygenation, whereas oxygen consumption depends on brain metabolism and oxygen extraction abilities.[12] A low $PbtO_2$ (<15 to 20 mmHg) is associated with worse outcomes and should trigger treatment.[13] $SjvO_2$ is an indirect measure of the hemispheric brain tissue oxygenation, as it provides the percentage of oxygenated haemoglobin in cerebral blood outflow on one side. The $SjvO_2$ normal range is between 55 and 75%.[14] Regional cerebral metabolism can be monitored using microdialysis. This technique measures glucose, lactate, pyruvate, glutamate and glycerol concentrations in samples of the brain extracellular fluid obtained through a parenchymal catheter. A high lactate/pyruvate ratio (>25, and especially >40) is a biomarker of reduced substrate delivery (perfusion deficit) and/or impaired oxidative metabolism (mitochondrial dysfunction).[15] The optimal target for CPP should be individually tailored according to the pressure autoregulation of CBF. The best CPP is the one at which the brain vessels react best to changes in pressure, within a range where pressure reactivity is preserved. This can be determined using indexes derived from the combined analysis of ICP or NIRS-derived parameters, and MAP.[16] Dynamic autoregulation can be measured by TCDU, looking at the correlation between CPP or MAP and CBF velocity.[17] Finally, *electroencephalogram (EEG) monitoring is recommended for seizure detection in all patients with impaired consciousness after an acute brain injury, after cardiac arrest, and in case of clinically evidenced seizures*.[1] Frequent intermittent EEG recording is a reasonable option, but, if available, continuous EEG (cEEG) monitoring is preferable because it can help detecting nonconvulsive seizures. EEG has also prognostic implications,[18] can detect an ongoing ischaemic problem in SAH,[19] and help assessing the degree of cognitive processing in unresponsive patients.[20]

Multimodal neuromonitoring integrating clinical examination, noninvasive and invasive physiological and imaging tools can potentially facilitate the early detection of secondary brain injury and early treatment of acute brain injury in critical care. Evidence is progressively emerging in current literature to support this approach as being beneficial for patients' outcomes.

How to protect the brain in nonneurological intensive care patients

Brain integrity can be compromised in other situations than after a direct insult.

One of the most important aspects of brain physiology is the pressure autoregulation of CBF. It corresponds to the ability of the brain to maintain relatively constant blood flow despite changing blood pressures. In healthy adults, the range of MAP where CBF is maintained constant is between 50 and 150 mmHg. Within this range, vasoconstriction occurs when MAP or CPP increases and vice versa. At the extremes, however, compensatory mechanisms fail, potentially leading to cerebral ischaemia at lower levels of perfusion or vasogenic oedema at higher levels. Pressure autoregulation occurs through myogenic, neurogenic, metabolic and endothelial mechanisms. These mechanisms may be impaired in some patients, hence prompting the need to adjust the MAP or CPP targets. For example, in chronic hypertensive patients, the range of MAP where CBF is maintained constant is displaced to higher values. In patients with stroke, traumatic brain injury, intracranial bleeding and other infectious and inflammatory conditions, autoregulation can be lost with potentially deleterious consequences, particularly if this alteration is associated with dysfunction of the blood–brain barrier. This underlines the utility of assessing autoregulation whenever possible in neurologically compromised patients, using the methods that are described above.

Sepsis-associated encephalopathy (SAE) is a severe neurological syndrome characterised by a diffuse dysfunction of the brain caused by sepsis, and not by a central nervous system infection.[21] It is probably the most common cause of encephalopathy in the ICU and occurs in up to 70% of septic patients. In this case, the release of pro-inflammatory cytokines causes a disruption of the blood–brain barrier, and an influx of immune cells and inflammatory mediators into the brain. This triggers the activation of microglia, which further releases cytokines and reactive oxygen species, leading to oxidative stress and neuronal damage. This pathological process may lead to brain dysfunction, impaired autoregulation and short-term and long-term brain damage. Clinical signs and symptoms of SAE include delirium and agitation, fluctuations in alertness and lethargy, as well as coma. SAE is associated with short-term mortality, especially in patients with a low Glasgow Coma Score (GCS), and those with long-term cognitive, psychiatric, physical and behavioural impairments. SAE diagnosis is challenging, insofar as diagnostic criteria have not been defined yet. In the context of SAE suspicion, any focal neurological sign warrants neuroimaging at least. Fever should be detected and treated, in parallel to the treatment of infections, and the development of secondary brain injury should be minimised by correcting anaemia, hyperthermia, metabolic imbalances and preventing delirium. Drug levels should be titrated to reduce the risk of neurotoxicity and benzodiazepines should be avoided. To avoid delirium, dexmedetomidine sedation is potentially an option,[22] particularly in ventilated patients with agitation.[23]

Cerebral oedema in the ICU is common, not only in neurological diseases, but also in nonneurological problems such as acute liver failure, hyponatraemia, diabetic ketoacidosis, acute altitude sickness, and more. *Cerebral oedema can be of cytotoxic, vasogenic, interstitial and osmotic nature. The clinical picture is variable, ranging from local to generalised neurological signs. One of the most dramatic causes of brain oedema occurs following acute liver failure in young patients with arterial ammonia levels higher than 200 μmol l^{-1}. The increase in intracellular glutamine leads to cell damage and swelling.*[24] *Treatment includes lowering the ammonia level, liver support, ICP monitoring and maintenance of CPP greater than 50 mmHg. Urgent liver transplant may be required in refractory cases. Diabetic ketoacidosis-associated cerebral oedema is mainly encountered in children and young adults. It follows a rapid insulin correction of glycaemia, which, in association with intravenous fluids, causes a rapid decrease in the effective blood osmolarity. This is responsible for a fluid shift into the brain tissue.*

Nonconvulsive seizures are frequent in ICU patients, and can be seen after a traumatic brain injury, stroke, SAH, drug withdrawal, encephalitis, tumours and irradiation, amongst others.[25] As indicated above, *their detection is only possible with cEEG monitoring*. Their clinical manifestations are variable and range between an altered mental status, anxiety, delirium, hallucinations, confusion, speech disturbances, lethargy and coma. Their treatment involves airway and ventilation control, haemodynamic support and administration of first-line, second-line or third-line antiepileptic drugs. *If not detected early and treated, nonconvulsive seizures in a comatose patient with structural brain damage are associated with poor prognosis and mortality*.

How to cure cognitive sequelae after brain injury with disorders of consciousness: any hope for the future?

Postcomatose disorders of consciousness (DoC) encompass different clinical entities. Coma is an acute state characterised by an absence of arousal and awareness. When the patient survives, coma can evolve towards an unresponsive wakefulness syndrome (UWS), formerly known as vegetative state, when patients show eyes opening but no signs of consciousness, and minimally conscious state (MCS), characterised by fluctuating but

undeniable signs of consciousness. When patients can functionally communicate or use objects, they are considered emergent from MCS (EMCS) and are no longer categorised under DoC.[26] These disorders place significant demands on the medical system, driving an urgent quest for effective treatments. Historically, the prognosis for DoC has been grim.[27] Only recently has there been active research to promote recovery, both nonpharmacologically and pharmacologically.

Nonpharmacological treatments include invasive brain stimulation, such as deep-brain stimulation (DBS) and vagal nerve stimulation (VNS). In a case report, thalamic DBS increased arousal and responsiveness in an MCS patient.[28] Another study showed that a UWS patient transitioned to MCS when receiving VNS.[29] In parallel, noninvasive brain stimulation (NIBS) studies have tried to obtain analogous results to the invasive options. Recently, thalamic stimulation has been achieved with low-intensity focal ultrasound pulsation (LIFUP), a NIBS that uses ultrasound to activate superficial and deep structures of the cortex. LIFUP has proven effective in some acute patients, with a randomised controlled trial underway.[30] Transcutaneous auricular VNS seeks to stimulate the vagal nerve through a branch in the external ear and tympanic membrane.[31] Other promising NIBS techniques include transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). tDCS has shown moderate positive effects when applied to the prefrontal cortex of MCS patients.[32] A recent multicentre study suggested that patients diagnosed with MCS and with a traumatic brain injury aetiology benefited from tDCS. However, the study was stopped on grounds of futility.[33] rTMS can stimulate cortical regions in a localised manner, aiming to unveil the role of specific regions for the emergence of consciousness.[34] Previous studies have shown a positive effect of rTMS for consciousness recovery.[35]

On the pharmacological side, amantadine, a dopaminergic drug used for Parkinson's disease, leads to a faster recovery from DoC,[36] and increases brain metabolism in several regions of the brain.[37] Another promising dopaminergic drug is apomorphine[38] that showed encouraging results in terms of behaviour, brain metabolism and neurophysiology. Furthermore, zolpidem, a commonly prescribed sleep medication, enhances arousal in around 5% of DoC patients, temporarily unveiling an enriched behavioural repertoire.[39] A more recent and controversial avenue of research explores the potential therapeutic use of psychedelics.[40] Through a boost of brain complexity, psychedelics are thought to induce transient amelioration of consciousness in DoC patients.

Although drug discovery has often been serendipitous, these accidental findings have led to systematic investigations and have informed theories, such as the meso-circuit hypothesis,[41] framing future research. This has pushed the role of computational modelling that aims to create an in-silico cerebral 'virtual homologue'. Such a method could allow for the stratification of patients, highlighting responsiveness biomarkers. Additionally, computational modelling might serve as a blueprint to perform virtual experiments that might be risky or difficult to perform in patients themselves. This approach could mark a shift towards personalised medicine, ensuring more efficacious treatments with minimised side effects and resource costs, ultimately benefiting the patients and the healthcare system.[42]

Although managing and treating DoC patients is a topic of ongoing debate, and so far, no definitive treatment has been found, there is no doubt that the field has taken a leap forward in the care of one of the most debilitating neurological conditions that modern medicine deals with. The future holds new vistas thanks to international collaboration and multicentric studies.

Intracranial pressure management: invasive monitoring and treatment of intracranial hypertension

Nowadays, ICP monitoring is considered a fundamental tool for the management of neurocritical patients. The brain is inside an inextensible box and, according to the Monroe-Kelly doctrine,[43] it is necessary to maintain a constant balance between the different components contained in that box, namely blood, CSF and brain matter. This equilibrium permits the avoidance of impaired CPP, cerebral ischemia and oedema with the subsequent risk of herniation.[44]

Indications for implementing ICP monitoring are based on clinical criteria, namely the GCS, and radiological criteria as found in brain CT or MRI.[45] ICP monitoring should be considered in case of traumatic brain injury with a GCS 8 or less and abnormal radiological findings like contusions, haematoma, oedema, herniation or compression of cisterns, or in cases of major head injury with GCS 8 or less and normal imagery, but with two or more abnormal features like SBP less than 90 mmHg, age older than 40 years, or bilateral or unilateral decorticate or decerebrate motor posturing. A GCS greater than 8 may still prompt the initiation of ICP monitoring if associated with large intracranial masses that could result in mass effect on surrounding structures or if the patient has to be sedated for trauma-related injuries.[46] The most recent guidelines of the Brain Trauma Foundation from 2016 [47] have downgraded these indications, because of the lack of strong evidence regarding a positive effect on outcome. This has been at the origin of clinical practice heterogeneity worldwide.[48]

The gold standard for ICP monitoring involves the insertion of a catheter into the lateral ventricles. The catheter is connected to a pressure transducer placed at the height of the external acoustic meatus (zero pressure reference). Another type of ICP monitoring is the placement of a sensor

into the cerebral parenchyma. The upper threshold limit for ICP to trigger treatment is traditionally between 20 and 25 mmHg,[49] but *the most recent guidelines recommend 22 mmHg, with target values for CPP between 60 and 80 mmHg.*[50] High ICP values correlate with unfavourable outcomes in patients with intracranial damage,[51] but the only randomised controlled trial on this topic failed to demonstrate that ICP monitoring can improve clinical outcomes.[52] However, this trial has been majorly criticised and possesses strong methodological limitations. *The recent SYNAPSE ICU study, a large observational study on the practice of ICP monitoring, has demonstrated an association between the use of an ICP monitoring-guided therapy of raised ICP and the 6-month patient mortality.*[48] Intracranial hypertension management should follow a gradual approach. The tiers of raised ICP treatment differ according to their level of aggressiveness and risk of side effects.[8] Tier 0 includes basic treatments to preserve cerebral homeostasis and physiology, such as maintenance of oxygenation and glycaemia within normal values, and 30° reverse-Trendelenburg chest position. Tier 1 requires the maintenance of CPP between 60 and 70 mmHg, a deepening of analgesia or sedation, normocapnia with arterial CO_2 partial pressure ($PaCO_2$) between 35 and 38 mmHg, and mannitol or hypertonic saline bolus administration. Tier 2 recommends moderate hypocapnia ($PaCO_2$ between 32 and 35 mmHg) and a MAP challenge to evaluate brain autoregulation for guiding CPP targets. Finally, Tier 3 includes the most aggressive treatments like decompressive craniectomy, controlled hypothermia and deep barbiturate sedation.

Choice of sedation in neurointensive care

Sedation in brain-injured patients is very frequently necessary, not only to allow supportive care safely and effectively, such as tracheal intubation and mechanical ventilation, but is also an integral part of treatment, consequent to its effects on brain function, metabolism and CBF. Despite the large use of sedation in moderate-to-severe brain-injured patients, *the currently available level of evidence to support one type of sedation regimen over another in a specific clinical situation is low*. When providing sedation, as with any other treatment, attention should be paid to potential negative effects, either generally or on the nervous system specifically. The general ones may include an increase in ventilation time and associated risk of pneumonia, an increase in length of stay or some drug-specific adverse events like propofol infusion syndrome (PRIS). Neurospecific side-effects may encompass decreased cerebral perfusion, mitochondrial dysfunction, impaired cerebral autoregulation, delirium and impaired neurological evaluation.[53] *Consequently, when choosing a sedative drug, it is mandatory to perfectly establish the balance between its advantageous properties and deleterious ones.*

Propofol and midazolam are frequently first-choice sedatives. They are equally well tolerated and effective regarding CPP and ICP control in brain trauma patients. The main determinants of choosing one over the other include availability, patient haemodynamic stability (hypotension being more frequent with propofol), the need for early clinical neurological evaluation (weaning of sedation is longer with midazolam), age (PRIS is particularly feared in paediatric patients), presence of severe or refractory elevated ICP (propofol may be more effective at lowering ICP because of a more pronounced effect on brain metabolism), cost (midazolam is cheaper) and clinician ease (most familiar drug should be used, to avoid drug-related complications of misuse). A combination of both drugs is sometimes necessary to combat tachyphylaxis, and because monotherapy is often not adapted to provide good-quality sedation in severely brain-injured patients with difficult ICP control.[54]

Studies investigating the use of opioids in traumatic brain injury are heterogeneous regarding drug choice and mode of administration. In patients with preserved cerebrovascular autoregulation, an opioid bolus is known to significantly decrease blood pressure, and increase ICP, without any significant effect on CBF. This is also the case in patients with impaired cerebrovascular autoregulation, meaning that, in addition to autoregulatory vasodilation, another mechanism exists to explain ICP elevation, possibly involving a change in cerebral metabolism and/or a direct opioid-mediated cerebral vasodilation.[55] *This acute effect on ICP is seen after a rapid de novo bolus but not after slower boluses. Opioid boluses prior to an invasive manipulation, like endotracheal suctioning, are ineffective to prevent ICP increases related to stimulation.*

Multiple studies have shown that ketamine does not increase ICP when combined with propofol or midazolam, and where normocapnia is maintained by mechanical ventilation.[56] Thus far, ketamine is increasingly considered an adjunct to standard sedation and is considered a good alternative to opioids to provide antinociception in brain-injured patients and spare vasopressor requirements.[57] Ketamine is also protective in specific situations, for example, when used to treat cortical spreading depolarisations that are associated to the progression of brain injuries.[58]

Even though dexmedetomidine has a safe profile regarding ICP, it weakens dynamic pressure autoregulation control, flattens CBF response to CO_2 and reduces CPP. Due to the paucity of available data and potentially deleterious effects on cerebral haemodynamics, it should probably be avoided during the acute phase of brain injury, while it may be useful in light to moderately brain-injured spontaneously breathing patients, or during the weaning phase from mechanical ventilation.[59]

Remimazolam is well tolerated and effective to induce and maintain general anaesthesia in frail patients. This new drug is promising for brain-injured patient sedation,

but its safety and advantages still need to be studied in this setting.

Muscle relaxants do not have any meaningful effects on brain metabolism and haemodynamics, but, knowing their long-term consequences on neuromuscular function, their use in brain-injured patients is usually avoided, except in situations where classical sedation does not allow smooth mechanical ventilation.

Temperature management after cardiac arrest

The role of temperature management in protecting the injured brain has long been a matter of intense debate but is now progressively approaching a consensus in the particular case of cardiac arrest.[60] Animal studies involving cardiac arrest models have shown remarkable benefits regarding neuronal damage limitation and neurological outcome improvement when moderate hypothermia in the range of 32 to 34°C is applied early after the return of a spontaneous circulation.[61] However, a direct transposition of these findings to humans is not straightforward. Some randomised controlled clinical trials show a statistically significant benefit for hypothermia in the range of 32 to 34°C as compared with normothermia or no temperature control in patients after cardiac arrest,[62] whereas other randomised controlled trials do not confirm this beneficial effect.[63] The question regarding which patients would benefit from lower (32 to 34°C) or higher temperatures is still not resolved.[64,65] Earlier and most recent meta-analyses of randomised clinical trials have shown a statistically non-significant effect in favour of hypothermia in the range of 32 to 34 °C.[66] *In the most recent and comprehensive Cochrane systematic review and meta-analyses including all randomised controlled trials, this beneficial effect of hypothermia in the range of 32 to 34°C as compared to normothermia or no temperature control was statistically significant.*[67] *The same conclusions can be drawn from several retrospective clinical studies, especially in subgroups with presumable moderate brain damage.*[66–74] *In addition, in this indication, 32 to 34°C hypothermia does not harm, thus not resulting in worse neurological or overall outcome.* Based on all those findings, we suggest that international guidelines follow the current Cochrane analyses. In the interim period, we suggest that clinicians consider hypothermia in the range of 32 to 34°C in all adult patients after cardiac arrest as soon as feasible, and maintain the temperature within this range for at least 24 h.[60] Active normothermia (36.5 to 37.7 °C) should be ensured after rewarming before and during neuro-prognostication, to avoid fever.[60]

The special case of subarachnoid haemorrhage

Aneurysmal SAH (aSAH) needs prompt diagnosis and treatment with endovascular coiling or surgical clipping of the aneurysm to prevent re-bleeding. Re-bleeding occurs most frequently during the first 24 h after aSAH.[75] Severe grade on admission (high radiological Fisher's grade),[76] large aneurysmal diameter and high blood pressure increase the risk of re-bleeding.

The optimal CPP to be targeted after aSAH and during its different phases is a matter of debate. Previous guidelines have suggested keeping the SBP less than 160 mmHg or less than 180 mmHg. Although these parameters may be reasonable to consider in practice, the available evidence is insufficient to recommend any specific BP target.[77] Aggressive management of blood pressure reduces the risk of re-bleeding, at the expense of an increased risk of secondary ischaemia. Higher blood pressures are advised after aneurysm securing to prevent delayed cerebral ischaemia (DCI), but the level of scientific evidence supporting this measure is not high.[78] Acute elevation of ICP following aSAH causes acute neurological deterioration. Noninvasive ONSD ultrasound measurement and TCDU provide rapid diagnosis of raised ICP and allow reliable follow-up. An ONSD greater than 5.6 mm indicates elevated ICP. Decreased diastolic flow velocity and increased pulsatility index (>2.13) as observed with TCD are indicative of possible raised ICP, whereas diastolic flow reversal indicates severely elevated ICP.[79] The early placement of an external ventricular drain and CSF drainage helps controlling ICP and restoring CPP, but it should be kept in mind that excessive and rapid CSF drainage causes an increase in transmural pressure gradient at the level of the aneurysm wall and may favour re-bleeding if the aneurysm is not secured by coiling or clamping.[80] CSF drainage reduces the risk of vasospasm, especially after severe aSAH (high Fisher grade).[81] Osmotic therapy with diuretics, mannitol or hypertonic saline can be used in combination with CSF drainage to control ICP and CPP, as well as transient mild hyperventilation to reduce CO_2 arterial partial pressure, while prolonged hypocarbia can lead to cerebral ischaemia. *Seizures develop at a rate of 10 to 20% in aSAH. It is recommended to initiate prophylactic anticonvulsant therapy in cases of aSAH with cerebral oedema or evident intracerebral or subdural haematoma.*[82]

The most important causes of neurological deficit after aSAH are vasospasms within the cerebral arterial circulation, and DCI. Vasospasm most commonly occurs between days 5 and 15 following bleeding, and high Fisher grades are associated with a higher risk of such complication.[83] Mechanistically, vasoconstriction is caused by the release of endothelin-1, which is triggered by haemoglobin degradation products, free oxygen radicals and neuro-inflammation.[84] Newly developed neurological deficits prompt the search for vasospasm. Any existing other potential causes of such deficits, like fever, leucocytosis and hyponatraemia, should not preclude from looking for it, insofar as those events can also be a consequence of vasospasm. The gold-standard for diagnosing a vasospasm is digital subtraction angiography. However, noninvasive TCD daily serial measurements at the bedside are recommended for early vasospasm detection, before its clinical manifestations, and for follow-up. It also helps determining the need for angioplasty in

severely affected patients. A progressive increase in MCA mean flow velocity (>80 cm s^{-1}) during the early stage of aSAH indicates vasospasm. Mild vasospasm is associated to velocity rates between 120 and 159 cm s^{-1}, moderate vasospasm to rates between 160 and 199 cm s^{-1} and severe vasospasm to rates over 200 cm s^{-1}. Symptomatic vasospasm is often seen at mean velocities of 160 cm s^{-1}.[79] The Lindegaard ratio corresponds to the MCA mean velocity divided by the ipsilateral extracranial internal carotid artery velocity. A Lindegaard ratio greater than 3 indicates vasospasm, between 3 and 5 mild vasospasm and >6 severe vasospasm.[85] Nimodipine is the only drug that has proven to be effective for the treatment of vasospasm. This calcium channel blocker dilates the arteries, reduces the calcium-induced excitotoxicity and decreases platelet aggregation. Nimodipine treatment should be started within 48 h after bleeding and continued for 21 days.[86] Early targeted fluid therapy, guided by preload and cardiac output monitoring, in severe aSAH patients reduces the risk of vasospasm and provides better functional outcomes.[87] As a positive fluid balance adversely affects survival in aSAH, the goal of fluid therapy should be euvolaemia. Vasospasm has been advocated as the underlying mechanism of DCI, but treating vasospasm fails to prevent it. Microcirculatory dysfunction, microthrombosis, neuro-inflammation, and cortical spreading depolarisation may play a role in the development of DCI after aSAH. Several potential mechanisms have been advocated as causing DCI, to find better treatment options, but the complete picture is still not clear.[88]

The special case of stroke

Stroke is not uncommon during the perioperative period and its occurrence can be favoured by several perioperative events: temporary antithrombotic or anticoagulant medications withdrawal in preparation to surgery, emboli secondary to cephalic arteries manipulations or endovascular and cardiac procedures, or low blood pressure episodes related to surgery and anaesthesia. The early identification of stroke can be challenging, particularly during and after general anaesthesia. Aside from classical symptoms, an abnormal delay of emergence, especially with tonus asymmetry, should prompt the search for a stroke. In this context, a local stroke suspicion procedure should ideally be clearly defined, involving a stroke neurologist as soon as possible, preferably before the first brain imaging. *Since no pathognomonic clinical sign or symptom may differentiate acute ischaemic stroke (AIS) from intracerebral haemorrhage (ICH), brain imaging is urgent when stroke is suspected, to differentiate between the two.* As most strokes (including peri-operative) are ischaemic, any suspicion of stroke should be considered as ischaemic until proven otherwise. The possibility of covert stroke, whose incidence can be as high as 7%, should be kept in mind.[89]

During the acute phase of an ischaemic stroke, the lying-flat position (although debated) [90] and the avoidance of high arterial blood pressure correction, unless necessary for a specific comorbid condition or blood pressure rises over 220/120 mmHg,[91] may favour cerebral perfusion and collateral recruitment in the brain circulation. After the acute phase, blood pressure management should be tight, to permit collateral recruitment in situations of absent or incomplete recanalisation, while limiting the risk of haemorrhagic complications.[91] Antithrombotic treatment commencement prior to the exclusion of an ICH should be avoided. In both AIS and ICH, hyperthermia, hypoxia/hyperoxia, and hypoglycaemia/hyperglycaemia should be avoided, or corrected if present.[92]

The first-line treatment of AIS is intravenous thrombolysis (IVT). Whenever possible, in the context of surgery, IVT should be initiated within 4.5 h after stroke onset.[93] Initiation after longer periods, up to 9 h, may be considered if perfusion imaging argues in favour of the presence of salvageable brain tissue existing (perfusion mismatch).[94] Strokes with unknown onset time, including those detected after recovery from anaesthesia, can also benefit from IVT if an ischaemic lesion is visible on the MRI diffusion-weighted images with no parenchymal hyperintensity on fluid-attenuated inversion recovery, which indicates that the stroke occurred within the previous 4.5 h,[95] or again, in situations of perfusion mismatch.[94] Whenever IVT is contraindicated, which is frequently the case after recent surgery, the alternative treatment is endovascular mechanical thrombectomy. Mechanical thrombectomy should be performed within 6 h of stroke onset, whether the patient received IVT or not. This approach significantly reduces the 'morbimortality' of AIS secondary to an anterior large vessel occlusion.[96,97] Mechanical thrombectomy can also be successful up to 24 h after stroke onset in patients showing radiological or clinical signs of salvageable brain tissue.[98,99] Thus, upon stroke identification and prior to treatment, appropriately tailored cerebral imaging is mandatory to distinguish AIS from ICH, screen for anterior large vessel occlusion, estimate stroke onset time when unknown and identify slow ischaemic stroke progressors (those with salvageable brain tissue).

The choice of the anaesthetic management technique during mechanical thrombectomy remains controversial. Randomised control trials and meta-analyses recently suggested that protocol-driven general anaesthesia, as compared with conscious sedation, may be associated with better recanalisation rates and functional outcomes.[100] *In any case, key anaesthetic goals should be shortening door-to-groin puncture and maintaining adequate blood pressure.*[101] Although the time-window for early revascularisation treatments has been extended, one should remind that 'having more time' does not mean 'taking more time' to initiate the treatment. The sooner IVT and/or mechanical thrombectomy are applied, the greater their efficacy and safety.

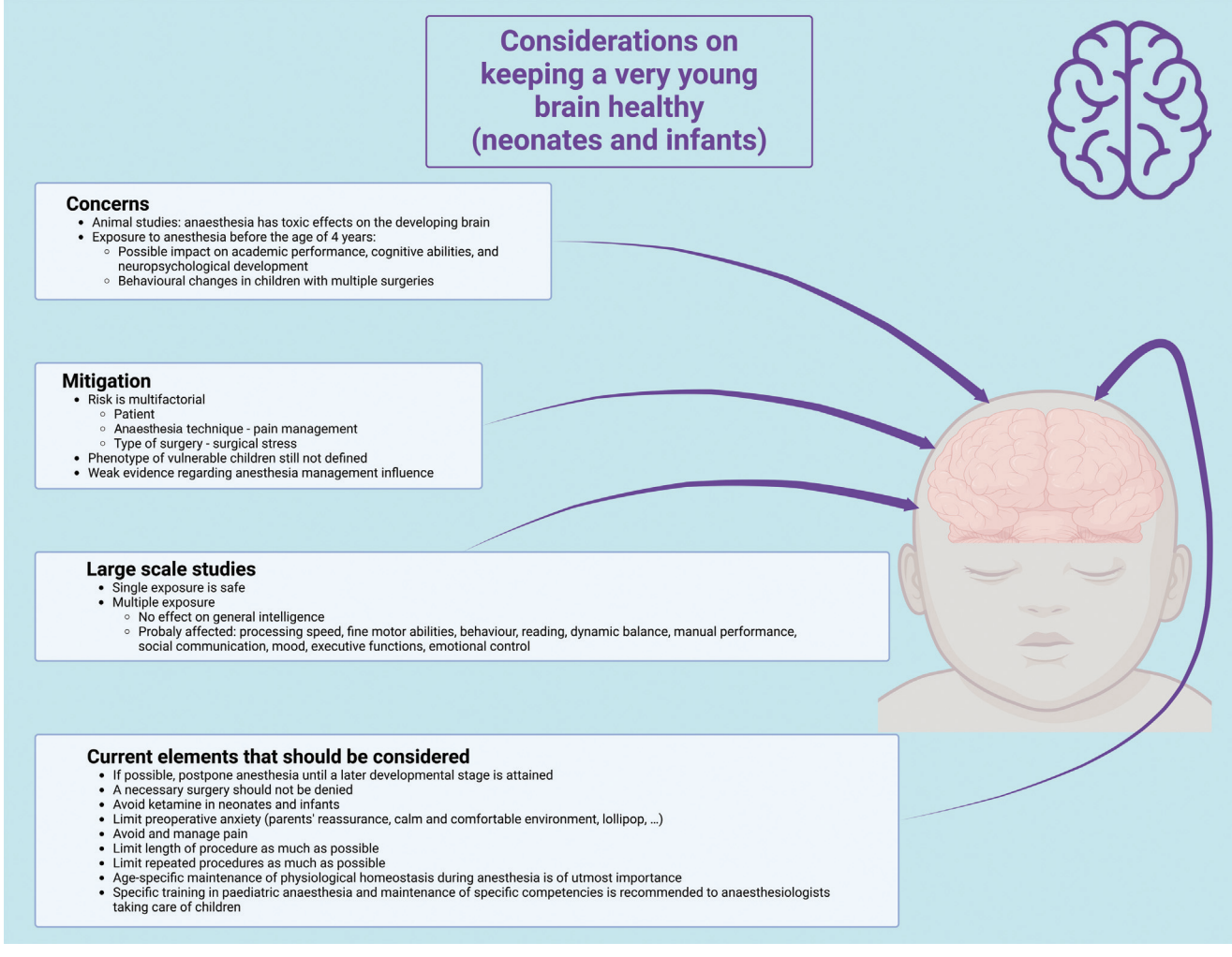
The early medical management of ICH aims at limiting haematoma progression. Therapeutic measures at that time include positioning the patient in a half-sitting position (debated),[90] *early aggressive lowering of arterial blood pressure to a systolic target less than 140 mmHg within less than 1 h*,[102] *stopping antithrombotic agents and reversing anticoagulants when present*.[92] Implementing intra-hospital goal-directed care bundle protocols with algorithms for the management of blood pressure, glycaemia, temperature and coagulation is currently being studied to explore whether it may improve ICH outcome.[103] Long regarded as being disappointing, the neurosurgical removal of the haematoma may soon find renewed interest with the minimally invasive approach of acute ICH.[104] As for AIS, neuroprotective interventions at the subacute phase of ICH still rely on the maintenance of normal oxygenation, temperature and glycaemia. *Hypothermia, corticosteroids and systematic antiepileptic prophylaxis are not recommended*.[92]

The prevention and early detection of stroke complications remains essential, because of their negative impact on outcome. Avoidance of unnecessary prolonged sedation and regular clinical assessment using the National Institute of Health Stroke Scale may improve the ability to detect complications. Special attention should be paid to the detection of deglutition disorders, insofar as they are a major cause of aspiration pneumonia.[92,105] After AIS in patients with atrial fibrillation, some algorithms based on the infarct volume or the clinical severity are useful to guide the timing of anticoagulation reinitiation, in order to limit the risk of symptomatic haemorrhagic transformation.[106]

How to keep a very young brain healthy (neonates and infants)

A graphical abstract of the key points delivered in this part is provided in Fig. 2.

Fig. 2 Considerations on keeping a very young brain healthy (neonates and infants).



What is the real impact of repeated surgery and anaesthesia in the very young?

In our daily clinical practice, providing anaesthesia in children is very common, although most anaesthesia lasts less than 1 h.[107] Assessing, recognising and managing anaesthesia risks are fundamental in establishing a well tolerated anaesthetic approach in children. Some of these risks are immediately visible such as sore throat, dental damage and cardiorespiratory events, whereas some others such as the potential neurotoxicity of general anaesthetics on the developing brain, are more difficult to quantify. Concerns of potential morbidities due to anaesthesia has emerged in the last two decades. Typical postoperative morbidity in adults, such as cardiac ischaemia, kidney failure and stroke, are very rare in children.[108] However, *children who have had major surgery for congenital abnormalities at very young age show impaired cognitive and physical developmental outcome at older age*.[109]

The neurodevelopmental processes in the human brain begin shortly after conception and continue to develop throughout childhood through several stages, in which γ-amino-butyric acid (GABA), and glutamate (through the *N*-methyl-D-aspartate or NMDA receptor subtype) neurotransmitters play an essential role.[110] Interestingly, all commonly used anaesthetic and sedative agents mainly act through a binding to either the GABA receptor (e.g. volatile anaesthetics, benzodiazepines, propofol, barbiturates and etomidate), or the NMDA receptors (e.g. nitrous oxide and ketamine).[111,112]

As early as 1999, increasing concern was raised following animal experiments with neonatal rats exposed to ketamine, nitrous oxide, isoflurane and midazolam, which demonstrated a significant increase in neuro-apoptosis in multiple brain regions, as well as long-term neurobehavioural deficits in learning, memory and discrimination in survivors.[113] Even though those studies were not demonstrating any contribution of surgical stress, untreated pain, inflammation and tissue trauma to neurodegeneration, the United States Food and Drug Administration first expressed warning in 2007 about the relevance of animal findings to paediatric patients and the need for further research.

Nowadays, a variety of clinical research projects in humans focus on the neurodevelopmental impact of single and multiple general anaesthesia exposures. The GAS study was performed on small infants without underlying abnormal medical conditions who underwent herniorrhaphy. The results demonstrated that *a single short general anaesthesia exposure of less than 1 h with sevoflurane does not increase the risk of adverse neurodevelopmental outcome at 2 and 5 years of age, when compared with awake-regional anaesthesia*.[114] *Another study on pair twins* [115] *and the large PANDA trial* [116] *also could not identify a difference between the neurocognitive function of exposed and unexposed children and their co-twins or siblings*. Moreover, a meta-analysis evidenced a large heterogeneity in methodology, definition, and intensity of exposure, outcome measures and time to follow-up between studies, and no difference in general intelligence in children exposed to a single general anaesthetic procedure compared with unexposed children.[117] Notwithstanding, there has been an increase in parental reports of behavioural problems. The MASK trial [118] investigated, in a large cohort, unexposed, singly or multiply exposed children to anaesthesia and found that the IQ did not differ significantly between groups. *In contrast, processing speed and fine motor abilities were modestly decreased in multiply but not in singly or unexposed children*. Parents of multiply exposed children reported increased problems with behaviour and reading but not with mathematics. Finally, in a recent large prospective cohort study,[119] all aspects of neurocognitive development were similar in unexposed, singly and multiply exposed children. Those who had multiple exposures had lower scores for dynamic balance, manual hand–fingers performance and social communication when compared with singly exposed children.

However, and importantly, one must acknowledge that brain impairment after surgery and anaesthesia is most likely to be a multifactorial phenomenon. Many contributing factors encountered during the perioperative period, and linked to patients, anaesthesia technique and type of surgery, have the potential to induce additional insult to the brain and affect neurocognitive outcome. *Current evidence shows no risk for a single exposure of less than 1 h to sevoflurane, and data are uncertain for longer exposures*. Repetitive exposure may expose to the risk of alterations in behaviour (mood disturbance, anxiety, depression), in executive functions (inhibition, planning/organising), and emotional control but not in intellectual performance.[120] The phenotype of vulnerable children still needs to be defined.

Finally, in the absence of alternatives, children should not be denied necessary surgery. Anaesthesiologists should carry on providing anaesthesia to children until further evidence and recommendations become available, and should maintain their expertise in paediatric anaesthesia practice.

General anaesthesia for surgery in the very young: how often is safe?

The issue of developmental anaesthesia neurotoxicity has been amongst the most debated topics of paediatric perioperative care over the past two decades. Although converging laboratory data suggest the possibility that the majority of commonly used general anaesthetics may interfere with neuronal development, there is no consistent human phenotype correlating with these findings. Despite the lack of human evidence for developmental neurotoxicity, *the US Food and Drug Administration has issued a 'Warning stating that exposure to these medicines for*

lengthy periods of time or over multiple surgeries may negatively affect brain development in children younger than 3 years'.[121] *Notably, these recommendations are not endorsed by many societies, including the European Society for Paediatric Anaesthesiology (ESPA) and the ESAIC.*[122]

Can we define a period of central nervous system vulnerability to general anaesthesia? From a biological perspective, each level of the highly orchestrated assembly of the nervous system may be vulnerable to anaesthesia exposure.[123] In humans, the neural plate is being formed during the second week of gestation. The proliferation and migration of neural cells alongside synaptogenesis follows and is actively ongoing during the first few years of postnatal life. Receptor signalling pathways, including GABAergic and glutamatergic systems, play a major role in these developmental processes and even short-term interference with the physiological patterns of these signalling mechanisms may have long-term consequences. As general anaesthetics are powerful modulators of these same signalling pathways, there is a biological rationale for their capacity to induce alterations in neuronal development throughout the whole prenatal period and well into childhood. *Despite this possibility, there are no convincing clinical data showing age-dependent effects of general anaesthetics on human brain development.*[124]

Preclinical data suggest that the extent of developmental anaesthesia neurotoxicity depends on the dose, the exposure length and/or the frequency of exposure.[123] In line with these observations, some but not all retrospective epidemiological data suggest that early-life multiple anaesthesia exposures are associated with an increased incidence of learning deficits.[124] Association, however, does not necessarily mean causality. Indeed, these epidemiological observations have many potentially major confounding factors. Amongst them, the child's medical condition necessitating surgery is a major one. It is highly plausible that the direction of cause and effect is mistaken in these studies as children with medical/neuropsychological abnormal conditions may necessitate more frequent surgery. In addition, in contrast to preclinical experimentation, the effects of anaesthesia, surgery and the associated perioperative stress responses are very difficult to separate in clinical investigations.[125]

In summary, it remains currently undetermined whether any specific periods of vulnerability to anaesthesia exposure during central nervous system development exist. Likewise, it is also unknown if repeated exposure to anaesthetics during early postnatal life is causally linked to subsequent neurocognitive deficits. Although we cannot formally exclude potentially harmful effects of anaesthetics on the developing brain, the lack of any clinically meaningful and reproducible phenotype provides some reassurance in favour of the safe use of anaesthetics in children.

Do's and don'ts when surgery is needed: choosing the best anaesthesia technique in the very young to protect the brain

The recent APRICOT[126] and NECTARINE[127] studies showed that critical respiratory and cardiovascular events are common during surgery in children and neonates, respectively. These studies concentrated on the perioperative period. APRICOT reported a low incidence of perioperative seizures and did not actively follow-up patients for other neurological sequelae. Emergence agitation is common after anaesthesia and has been shown to be associated with rapid emergence from rapidly acting volatile agents such as sevoflurane. It is particularly common among children from 2 to 5 years of age, undergoing painful surgery, and those patients with preoperative anxiety, and/or specific behavioural traits. It can be prevented and treated with intravenous dexmedetomidine infusions. The long-term consequences are not known.

In numerous animal studies, neonatal exposure to multiple anaesthetic agents has been shown to cause neurotoxicity and neurobehavioral changes. Retrospective epidemiological studies in humans have shown inconsistent results. *Well conducted, prospective studies involving adequate controls have failed to convincingly show evidence that early exposure to anaesthesia is associated with impaired neurological development*. Examples include the PANDA study,[116] involving matched controls, and the GAS study,[128] a randomised controlled trial, in which neonates requiring inguinal hernia repair were randomised to undergo the procedure under either regional anaesthesia or general anaesthesia with sevoflurane. *There is thus no strong evidence to favour any anaesthetic technique*. Current research should aim at determining the best anaesthetic management in this patient population, as a function of the considered surgery, and at determining whether the use of tools such as the EEG improves anaesthetic delivery, detection of complications and outcome.

When surgery is needed, the current focus should be on good perioperative anaesthetic care, provided by appropriately trained and experienced anaesthesiologists in paediatric anaesthesia, ideally in specialised paediatric centres for small children undergoing complex procedures. At present, the optimal way to protect the brain is thus to take measures to limit preoperative anxiety, prevent and manage pain, avoid harm and maintain normal physiological homeostasis. Although normal ranges of core temperature, blood glucose, blood electrolytes and arterial oxygen and carbon dioxide tension have been known for a long time, it is only recently that well validated age-related and weight-related arterial pressure norms have been determined. To facilitate optimal and safe care, various organisational aspects should be addressed. To ensure competence of the involved anaesthesiologists, and organisational competence, there should be harmonisation of training curricula and standards, international quality

assessment and improvement projects, healthy dialogue/communication between professional bodies and public stakeholders.

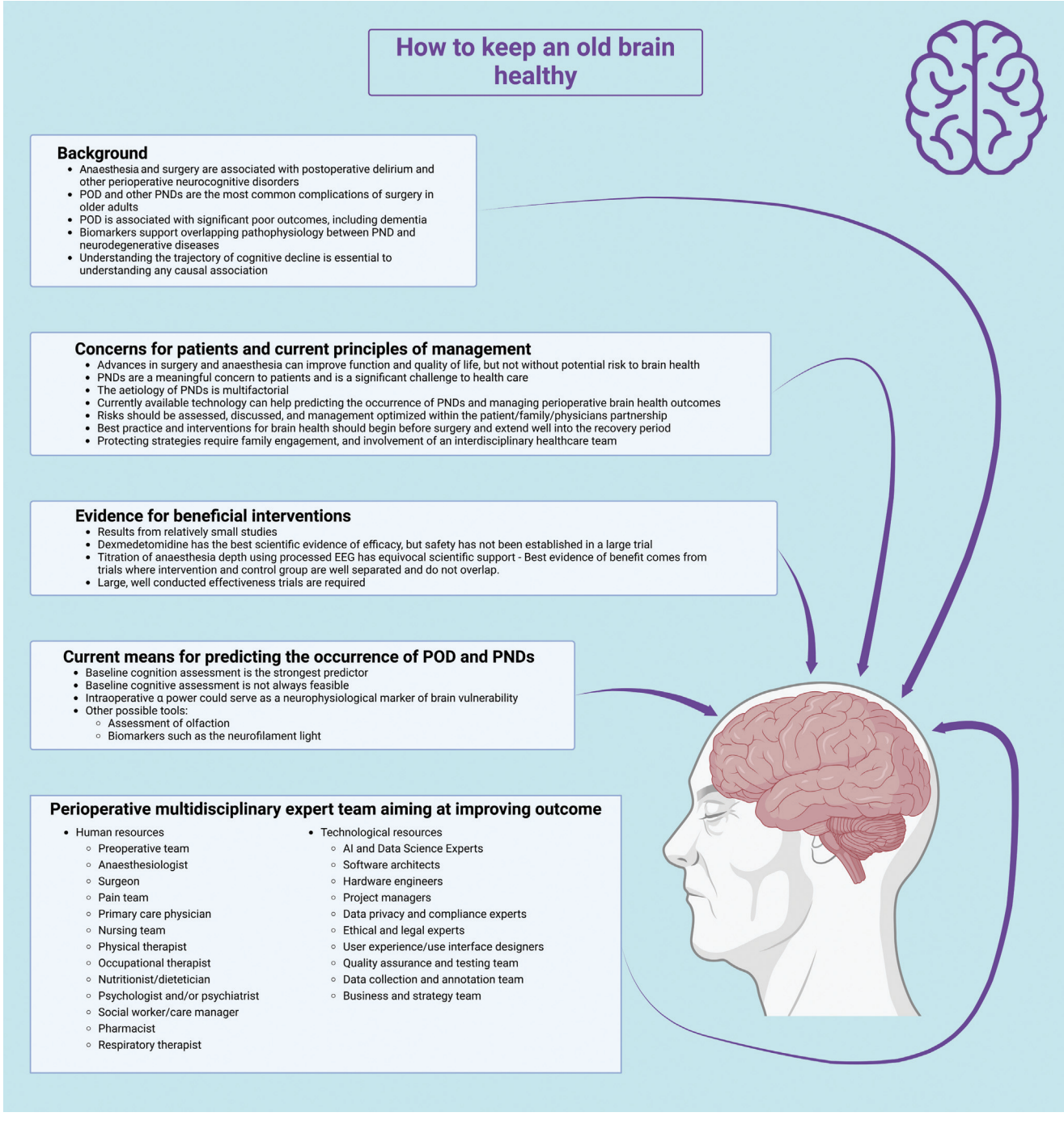
How to keep an old brain healthy

A graphical abstract of the key points delivered in this part is provided in Fig. 3.

Perioperative identification of patients at risk of postoperative brain dysfunction

Perioperative neurocognitive disorders, including postoperative delirium (POD), and delayed neurocognitive recovery up to 30 days after surgery (dNCR) and postoperative neurocognitive disorders (PNDs) up to 12 months after surgery, are common postoperative complications

Fig. 3 How to keep an old brain healthy.



PND, postoperative neurocognitive disorder; POD, postoperative delirium.

among those 65 years old or more, and may occur in up to 53% of patients.[129] Although POD and dNCR are two different entities, they are thought to share common pathophysiological mechanisms.[130] Identifying patients at risk of PND is important, because PNDs may have substantial functional, emotional, and psychiatric impact on the patients,[131] and are potentially preventable in many cases.

Baseline cognitive impairment is a strong risk factor for PND,[132] among others less direct risk factors like the surgery-induced increase in blood–brain barrier permeability.[133] Hence, several factors influence the occurrence of PNDs, which are predisposing (age, preexisting cognitive impairment, depression, multimorbidity, impaired functional status, frailty/malnutrition, sensory impairments, chronic alcohol, . . .) or precipitating (major surgery, emergency, postoperative complications, pain, . . .).[134] *A baseline cognitive assessment has been recommended by the American Society of Anesthesiologists (ASA) Perioperative Brain Health Initiative and by the ESAIC, to advocate screening to identify at risk patients*.[135] A preoperative cognitive assessment using a complete battery of neurocognitive tests is the gold standard, but it requires expertise, manpower and is time consuming. Other tools may thus be helpful in this respect, such as the frontal EEG. Indeed, decreased intraoperative frontal alpha power correlates with baseline cognition, and is associated with the occurrence of POD,[136] and the severity of postoperative subsyndromal delirium.[137] Furthermore, lower intraoperative EEG alpha power has been associated with an increased incidence and duration of EEG burst suppression,[138] and in turn with an increased POD risk.[139] This observation holds especially true if burst suppression occurs at low anaesthetic doses.[140] Alternatively, plasma biomarkers such as neurofilament light (NFL) may indicate at baseline a patient's brain vulnerability, and may thus identify patients at increased risk of POD.[141] Recently, other tools such as olfactory performance have emerged as potential determinants of brain vulnerability.[142] Worse baseline olfaction is associated with impaired cognition as well as increased perioperative concentrations of plasma NFL.[143] The combination of predictive tools may lead to the availability of sensitive and specific algorithms to better assess the risk of POD in individual patients. *It is currently recommended to evaluate cognitive reserve before anaesthesia and surgery, using simple and well known cognitive screening tests such as the Mini-Cog, the Mini-Mental State Exam, the Montreal Cognitive Assessment test or the Clock-Drawing test*.

The role of anaesthesia and surgery in damaging the old brain: a top-down approach

Surgery and anaesthesia are associated with complications in elderly patients. Among them, serious neurological complications such as POD, stroke and covert stroke, and cognitive decline are surprisingly common.[144] Up to now, clinical understanding, risk communication and research on cognitive disorders have been relatively neglected compared with other organ system complications. Understanding these disease processes has traditionally had a bottom-up mechanistic focus, from the underlying potential mechanisms to possibilities of treatment. Consequently, many of the interventions that are proposed to prevent or treat these complications are complex or have multiple putative mechanisms of action. A top-down focus on clinical trial data may allow the early identification of effective measures, with the mechanistic understanding coming later. Among the interventions that may contribute to preventing or reducing the incidence of these complications, some, such as multimodal analgesia (with paracetamol, NSAIDs, . . .) or comprehensive geriatric screening, have a surprisingly limited evidence base. There is a need for identification of therapeutic interventions, and of the most effective components of screening and preoperative optimisation. Currently, the use of regional anaesthesia and the avoidance of benzodiazepines or gabapentanoids are proposed as beneficial measures, although the literature sometimes appears controversial in this respect.[145–148] *The strongest evidence for the benefit of perioperative measures concerns dexmedetomidine and its positive effects on reducing the occurrence of POD, demonstrated in randomised controlled trials and meta-analyses*.[149] A top-down approach also evidences separate potentially beneficial intermediate endpoints, whose avoidance might be beneficial in reducing the risk of POD and stroke, such as hypotension, hypertension, bradycardia, tachycardia, hypoxaemia and neuro-inflammation. These are some plausible targets, but strong evidence of efficacy has not been well demonstrated yet. Large effectiveness and safety trials are required to identify populations where these parameters demonstrate efficacy, while putative mechanisms are explored. This top-down approach will minimise delays to determine effective brain protective measures in clinical practice.

Processed EEG (pEEG) titration of depth of anaesthesia to prevent POD is an intervention with equivocal results from randomised controlled trials.[150] A beneficial effect can be explained be several plausible mechanisms, including GABAergic anaesthetic agents dose reduction, effects on neural networks, interference with neurotransmitter pathways (e.g. the cholinergic system), reduction in neuro-inflammation, and direct or indirect effects reducing covert stroke. In such studies investigating pEEG-guided titration of anaesthetic agents, in addition to clinical and population heterogeneity, there is heterogeneity regarding adherence to the intervention, with sometimes very small between-group difference in pEEG index values. Trials with large differences in index pEEG values and the smallest overlap in anaesthesia exposure between intervention and control group show large treatment effects, and potentially explains the lack

of benefit in some studies, and the lack of strong evidence of efficacy for now.

Anaesthesia, surgery and dementia: is there a link?

As mentioned above, postoperative cognitive disorders include POD, dNCR and PNDs, which regroup postoperative mild and major neurocognitive disorders (postoperative NCD) that persist for up to 12 months after the procedure in a significant proportion of older individuals.[151] Postoperative NCD, mild and major, align with mild cognitive impairment (MCI) and dementia, respectively, and are associated with increased mortality, morbidity, loss of independence, psychosocial detriment and significant social and economic costs. It is now well established that POD is associated with a significant (12-fold) increased risk of dementia. Prevention of POD would not only improve patients' recovery trajectory but also reduce the prevalence of dementia in the community. As the global population ages, more older people undergo anaesthesia and surgery every year, with 50% of all anaesthetics expected to be administered to those aged 65 years or more by 2050. This demonstrates the large proportion of the population exposed to these risks every year. POD reflects an acute form of brain dysfunction and is associated with long-term poor outcomes including increased risk of dementia, increased risk of institutionalisation, neurodegeneration and increased morbidity and mortality. Other, less dramatic forms of PND manifest as cognitive impairment, which also impair recovery and impact quality of life. Up to 30% of patients will progress to dementia within 7.5 years following cardiac surgery. Changes in Alzheimer's disease biomarkers are associated with PND, suggesting overlapping pathophysiology. The most plausible mechanism is a peripheral inflammatory response to an acute insult (surgery) leading to neuro-inflammation through increased permeability of the blood–brain barrier, allowing entry of cytokines and other humoral agents, eventually leading to neuronal damage, especially in a 'vulnerable' brain.[152]

How to prevent postoperative brain dysfunction: a perioperative approach

Over 300 million surgical procedures are performed each year worldwide.[153] *The most common complication after surgery is a brain dysfunction disorder.*[154] Perioperative neurocognitive disorders include cognitive deficits that can last for up to 1 year after the patient has had a procedure, involving surgery and anaesthesia.[151] The population aged 60 years old or more is expected to double in the next two decades, and this age group accounts for nearly half of all surgical procedures.[155] This fact is a major challenge to the WHO's declaration: *'To foster healthy ageing and improve the lives of older people, their families, and communities, fundamental shifts will be required not only in the actions we take but in how we think about age and ageing'*.[156] Anaesthesiology departments occupy a central role in advocating for and requiring a massive shift towards a multidisciplinary and multimodal healthcare system when it comes to prevent postoperative brain dysfunction. Furthermore, at least some of this suffering and expense should be avoidable, which has major moral, ethical and financial implications for our global healthcare systems.

Research in the last few decades has demonstrated high-quality evidence that helps inform best practices for brain health throughout the perioperative period.[135,154,157–160] For now, however, it is unlikely that one isolated intervention will dramatically change the course of perioperative neurocognitive disorders. A comprehensive and continuous bundle of interventions can be implemented with the goal of keeping the ageing brain healthy.[157] The first of which is readily available, but requires that multiple teams, communities, and healthcare professionals focus their efforts on perioperative programs that are feasible, well tolerated, and targeted to patients most at risk, such as older adults. The creation of patient-specific programme pathways, which extend throughout the perioperative period, can limit both the incidence and severity of brain dysfunction after surgery and anaesthesia and warrant the involvement of a multidisciplinary team.

Recent technological advances have made the development of digital tools possible; those that can be pragmatically and continuously used by healthcare providers to decrease bias, fatigue and distraction. Artificial Intelligence systems can integrate data from various sources, including the electronic health records, risk stratification scores, intraoperative monitoring devices, wearable sensors, biomarkers and medical imaging to provide a comprehensive picture of the patient's perioperative brain health as well as a comprehensive view of a patient's perioperative journey. This comprehensive approach can improve the identification of at-risk populations and complications to track patients' progress, expedite interventions and enhance patients' safety and health. For these programs to work, we need to shift from a traditional system of healthcare delivery to one that involves more professionals (previously outside the domain of current systems), to successfully integrate programs that focus on improving and maintaining the brain health of our ageing patient population.

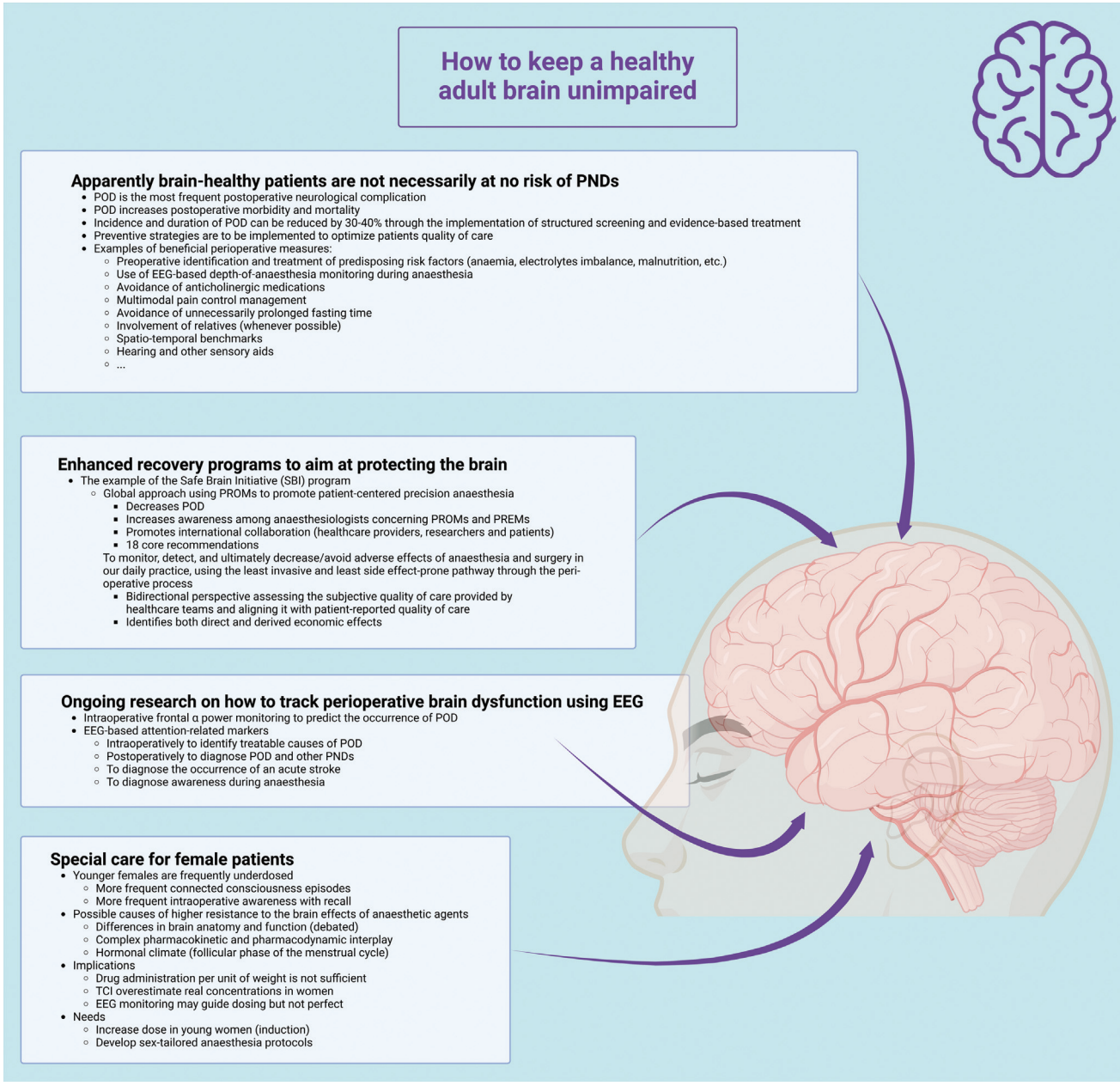
How to keep a healthy adult brain unimpaired

A graphical abstract of the key points delivered in this part is provided in Fig. 4.

Do's and do not's during anaesthesia for protecting the brain

Responsible medicine places the characteristics of trustworthiness, usefulness and ethics at the centre of inpatient care. These characteristics are of great importance for vulnerable patients, who form an increasingly growing

Fig. 4 How to keep a healthy adult brain unimpaired.



EEG, electroencephalogram; PND, postoperative neurocognitive disorders; POD, postoperative delirium; PREMs, patient-related experience measures; PROMs, patient-related outcome measures; SBI, Safe Brain Initiative program.

patient group due to demographic change and pose new challenges for the healthcare system. *POD is the most common postoperative complication in older patients.*[161] *POD is an acute organ dysfunction of the brain that manifests itself in attention disorders, impaired consciousness and logical thinking disorders with a fluctuating course. It occurs during inpatient treatment but is also prognostically relevant for postinpatient quality of life and survival.*[162] Delayed initiation of treatment leads to increased mortality within the first 90 days[163] and to an increased need for postinpatient care.[164] Neurocognitive disorders also occur in a quarter of affected patients over the long-term.[164] Precipitating and predisposing risk factors, which are particularly present in older patients, increase their vulnerability to POD. Each patient has an individual POD risk, which leads to the development of POD within the first 5 days after surgery if a threshold value is exceeded.[135] Preventive measures for patients with risk factors should be implemented during this time window.[165] *POD incidence and duration can be reduced (or number of POD-free days*

increased) by approximately 30 to 40% when a structured screening of patients at risk, and an evidence-based bundle of preventive interventions and comfort measures are implemented.[135,166–168] *Quality requirements for the best possible care are already defined in the European and national evidence-based and consensus-based guidelines.*[135]

Due to the increasing life expectancy of the population and medical advances, more and more complex surgical procedures are being performed on older and sicker patients. This is accompanied by higher demands on the indication for surgery, patient safety and the quality of postoperative care. The increasing life expectancy of the population is very clearly reflected in the healthcare sector. In Germany, the number of surgical procedures performed on increasingly older patients is rising steadily. Out of a total of 60 million operations and medical procedures performed on an inpatient basis in 2017, over half of the operations and procedures (31.4 million) were performed on patients over the age of 65 years old. In 2018, these figures had risen even further to 32.2 million. With this trend, it is to be expected that older patients will continue to account for the largest share of inpatient care in the future and have a special need for care. It is, therefore, important to align inpatient care structures with the needs of patients. This includes a holistic concept of POD management that integrates preventive measures both preoperatively and especially in the perioperative setting. In this respect, the use of EEG-based monitoring to control anaesthesia depth is possibly useful. Other measures may serve to optimally prepare the patient for the operation; preoperative identification and targeted treatment of POD risk factors (e.g., anaemia, electrolyte imbalance, cognitive deficits and malnutrition), avoidance of drugs with anticholinergic properties, application of multimodal pain management, and investment in nonpharmacological preventive measures (e.g. provision of aids for sensory deficits, shortening of fasting time to 2 h for liquids, with eventual sonographic control of gastric emptiness before induction, involvement of relatives at all steps of the perioperative course, including in the ward, at induction of anaesthesia, in the recovery room and in the ICU, etc.).

POD prevention measures contribute to improve patient safety if they are applied holistically. Their implementation, according to current guidelines, necessitates the removal of barriers to make the systems more transparent for patients and caregivers. The cross-departmental digitisation of processes may help to build a coherent interdisciplinary, multiprofessional and transparent care pathway.[169] In view of the increasing clinical workload, this has the potential to increase efficiency, provide relief and close the current gaps in inpatient care.

Novel electroencephalogram-based monitoring approaches to prevent brain injury under anaesthesia

EEG-based depth of anaesthesia monitors have been in use for decades, and their applicability for detecting awareness during general anaesthesia is under debate.[170] Other usages for these monitors have also been discussed widely, including regarding the reduction of POD and on a smaller, yet important scale, the prevention of PND and long-term mortality.[171] *It seems reasonable to conclude by now that, with regard to reducing intraoperative awareness with explicit recall, these monitors are useful, particularly when total intravenous anaesthesia is used,*[171] *but not superior to an end-tidal vapor concentration lower limit alarm when inhalation anaesthesia is used.* The interpretation of the index value they provide is impeded by several confounding factors, including the electromyographic activity of facial muscles.[172–174] Multiple studies have tested the ability of these monitors to reduce the incidence of POD.[140,175] When used for limiting the occurrence and length of very deep anaesthesia episodes, with or without burst suppression, it seems that they are successful.[150,176–178] However, in studies where the mean depth of anaesthesia of the control group was not that low, for example, because other means were used to limit the occurrence of very deep anaesthesia, the added value of EEG was less evident.[175] Indeed, several factors other than deep anaesthesia may contribute to POD, including postoperative intervening elements like pain, infection, specific medications and length of stay in the ICU,[179] as well as intraoperative factors like surgery duration, blood loss and transfusion and electrolyte imbalance.[180,181] All these factors have more impact on patients with preoperative risk factors (e.g. elderly, diabetic, and depressive patients, patients with cognitive impairment, cerebrovascular disease, pulmonary disease and those on chronic opioid use).[182–184] Unfortunately, we currently do not have the wherewithal to identify and predict POD due to these multiple factors. However, there is a strong need for such an ability, as *under-diagnosis of POD is known to have a significant impact on clinical outcome, with more complications and delay in recovery.*[185]

The hallmark of POD is severe inattention.[186] Studies with event-related potentials (ERP) during delirium, mainly with attention-related markers, were reported in the past.[187] However, the 'classical' EEG/ERP attention-related markers might be cumbersome to extract, as they often involve the use of multiple scalp electrodes and/or long sample duration for generating a single value. This renders them somewhat less practical for real-time monitoring. Over the last couple of years, some novel attention-related EEG-based markers have been described, which can be extracted from a single EEG-based channel [188,189] and measured in real-time during anaesthesia.[190] It might be possible to monitor for the potential evolvement of POD also under anaesthesia using those attention-related EEG markers, and identify any co-occurring, underlying and potentially treatable causes.[191] Insofar as attentional processes are spread and involve many brain modules, the injury of several brain areas might impact attention. As such, major acute stroke is

likely to be detectable via prefrontal monitoring of attention as well.[192] PND overlaps in underlying mechanisms with both stroke [193] and POD,[194] and inattention is a common dysfunction of PND as well.[195] Therefore, the intraoperative recording of attention-related markers might also identify situations potentially leading to PND, and guide effective intervention to counteract reversible causes, for improvement of outcome.

Selective attention markers, related to the perception of external stimuli, seem to persist even during surgical levels of anaesthesia, while markers of more sustained attention are reduced.[196] When markers for sustained attention increase during anaesthesia, it might indicate awareness.[190] Such markers might transcend all types of anaesthetic drugs and protocols and might not be significantly impacted by EMG activity, or its lack.

Taken together, effective monitoring of attention under anaesthesia might offer the breaking of the 'glass ceiling' of current EEG monitoring, identifying not only too deep or insufficient anaesthesia but also the other factors that might lead to postoperative brain dysfunction. Obviously, more studies are needed to assess this novel approach.

The role of enhanced recovery programs for protecting the brain

Enhanced recovery after surgery (ERAS) protocols represent a meticulous, evidence-based approach to perioperative care, geared towards attenuating the surgical stress response, optimising physiological function and expediting recovery.[197] Although these protocols have demonstrated substantial benefits across various surgical specialties, their implications for brain health have recently emerged as a focal point of interest.

Systemic inflammation, a well acknowledged contributor to central nervous system dysfunction, has been notably linked to postoperative cognitive decline,[198] a concern that is especially pertinent among elderly and frail patient populations. A mounting body of evidence suggests that surgery-induced systemic inflammatory mediators can exert influence on brain function, potentially culminating in cognitive impairment, especially among vulnerable patient cohorts. To comprehend the molecular underpinnings of this intricate relationship and discern the precipitating and modulating factors at play, it is imperative to develop strategies that safeguard the brain during the surgical and perioperative journey. The Safe Brain Initiative (SBI)[199] represents a holistic approach harnessing Patient-Reported Outcome Measures (PROMs) to elevate patient-centred precision anaesthesia and preempt POD and PND. Through systematic collection, analysis and real-world precision data provision, the SBI effectively bridges the feedback gap in perioperative care. Key objectives encompass delivering efficacious anaesthesia and patient-centred perioperative care, gauging patient and team satisfaction, scrutinising environmental sustainability impact, and ensuring economic efficiency. Founded upon international guidelines,[135] the SBI has introduced an 18-core recommendation care bundle designed to confront and prevent potential complications and challenges associated with anaesthesia and perioperative care. Initial outcomes have demonstrated a remarkable reduction in POD incidence within routine care settings, concomitant with heightened awareness among anaesthesia team members concerning PROMs and Patient-Reported Experience Measures (PREMs). Patient-centred precision care initiatives like SBI, alongside enhanced recovery programs such as ERAS, epitomise innovative and cost-effective approaches geared towards augmenting the quality of perioperative care. Through the integration of PROMs, PREMs, PND assessments and systematic feedback mechanisms, particularly within the ambit of the SBI, these initiatives are poised to advance the realm of patient-centred precision perioperative care, thereby enhancing patient outcomes and equipping anaesthesia practitioners with comprehensive knowledge. International collaboration among healthcare providers, researchers and patients plays an indispensable role in shaping the future of anaesthesia practice, with a resolute focus on maintaining patient-centred precision care and safeguarding the brain, as exemplified by initiatives like ERAS protocols and SBI. The embrace of these approaches holds the promise of elevating patient outcomes and deepening our understanding of brain protection within the perioperative setting.

Are there sex differences in the sensitivity of the brain to anaesthesia?

Anaesthesiologists take care of a multitude of patients with very different characteristics. In this context, anaesthesiologists face huge inter-individual variability regarding the dose–concentration–response relationship of anaesthetic medications. Inter-individual variability comprises pharmacokinetics, sensitivity to the effect of agents and interactions between medications. Hence, prediction of an effect in an individual, particularly at the brain level, is not easy. Current means for guiding anaesthetic agent dosing include boluses and continuous infusions per unit of weight and time, target-controlled infusions (TCI) and measurement of effect – mainly through the EEG. These means are far from being perfect. Among factors potentially influencing dosage, sex is generally neglected.

Recent studies have shown that the odds ratio of awareness episodes during general anaesthesia in female individuals as compared with males is 2.09 (and even higher in younger patients),[200] and is 1.38 regarding awareness with recall.[201] Time to recovery is also approximately 2 min shorter.[201] Hence, female individuals might be more resistant than male individuals to the brain effect of anaesthetic agents, rendering them at risk of unpleasant events with deleterious consequences. Theoretically,

and aside from evident genetic factors, the reasons for such differences can be related to differences in brain anatomy and physiology, in pharmacology and in hormonal climate.

It has been known for a long time that, after childhood, the brain size starts to differ between female individuals and male individuals, being 10% larger in male individuals. The differences are more marked in brain structures with a high density of sex steroid receptors (caudate nucleus, amygdala, hippocampus and cerebellum).[202] Some sex differences in brain functioning and physiology, notably regarding memory encoding, have been evidenced, mainly in animal studies.[203] Transposition of this to humans is not straightforward, and the debate on this topic is currently intense. For some authors, there is considerable overlap between female individuals and male individuals in terms of brain volume, connectivity and activation of regions during tasks, and eventual differences are negligible after correcting for brain volume.[204] For them, sexual dimorphism of brain anatomy and physiology is not a reality. Others advocate subtle differences, both in terms of cognition, behaviour and connectivity,[205] as well as a differential sensitivity to brain diseases.[206]

Clear sex-related pharmacological differences exist. Body composition and distribution volumes are not the same in male and female individuals,[207] and calculation of them are not necessarily managed the same way in the available TCI models.[208] There exists an oestrogen-dependent increase in protein binding during the follicular phase of the menstrual cycle, and female individuals may have different enzymatic activity and hepatic drug elimination than male individuals.[207] Differences in cardiac output and liver perfusion may also contribute to modified drug pharmacokinetics. Consequently, the same propofol infusion scheme leads to lower concentrations in female individuals.[209] Demonstrating a real difference in the pharmacodynamic effect of drugs is not evident. Again, for propofol, although TCI target concentration for loss of consciousness (LOC) is usually higher in female individuals, measured concentrations at that time are identical to male individuals, indicating that TCI models often overestimate real concentration in female individuals.[210] Similarly, sevoflurane concentrations at LOC are identical in both sexes.[211] Hormonal climate plays a role in determining anaesthetic requirements. These are higher during the follicular phase for volatile anaesthetics and propofol, probably through an allosteric modulation of GABA receptors, a potentiation of NMDA receptor-mediated glutamate neurotransmission, and an inhibition of endogenous sleep mechanisms by oestrogens.[212]

In conclusion, female individuals are frequently underdosed. This is because of complex pharmacokinetic and pharmacodynamic interplays. Measuring the effect of our drugs with the currently available monitors is probably not a solution to this problem, because they are not sensitive and specific enough. We, therefore, should certainly increase doses in female individuals, particularly at induction, and aim at developing sex-tailored anaesthesia techniques.

Does monitoring the brain in the operating room and in the intensive care help keeping it healthy?

A graphical abstract of the key points delivered in this part is provided in Fig. 5.

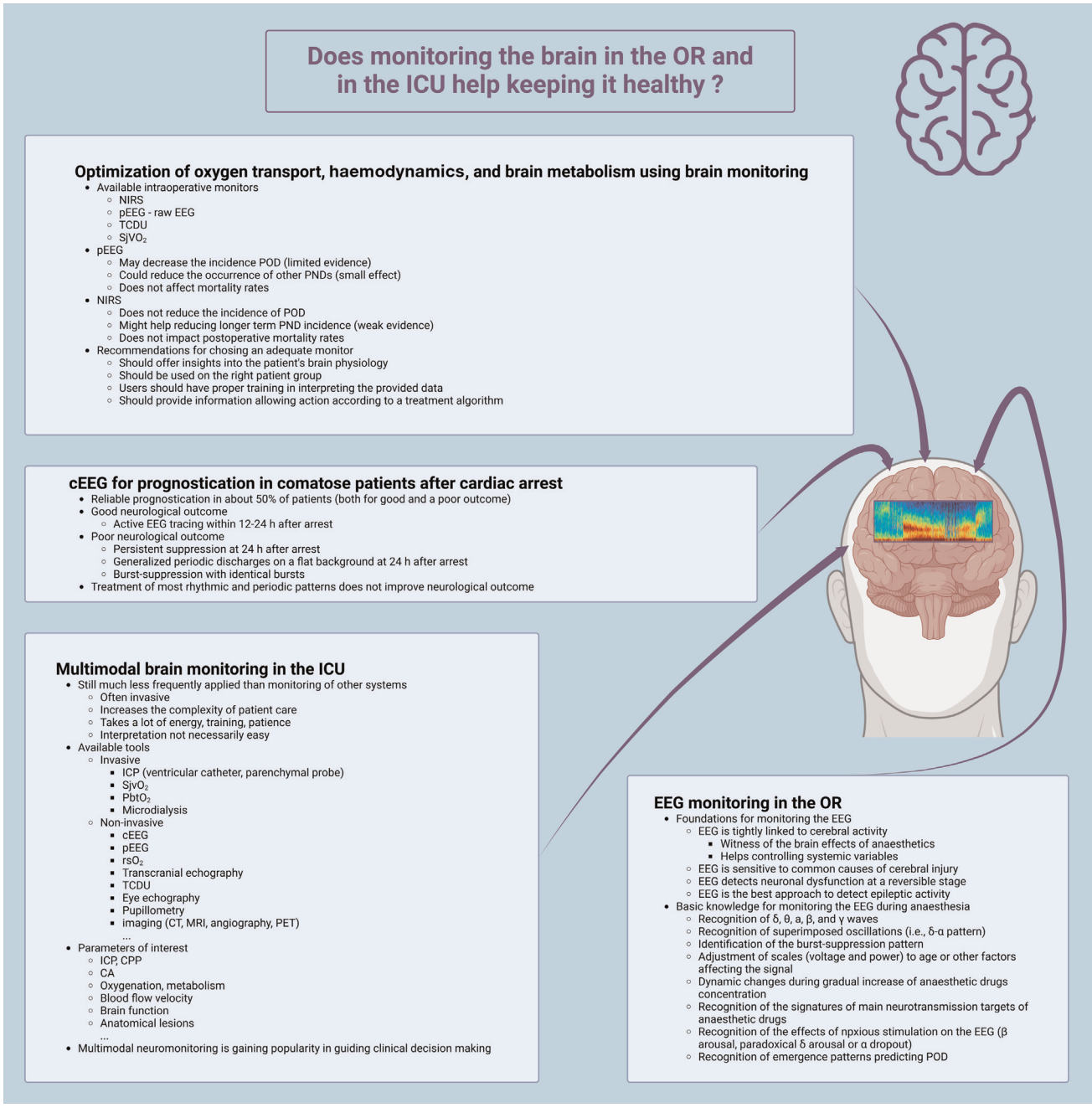
Clinical examination remains a fundamental component of neuromonitoring in the intensive care unit, in the operating room and during the postoperative period

In the ICU, the primary clinical parameter that should be monitored is the patient's level of arousal and awareness, using, for example, the GCS.[213] *In the operating room, clinical signs of the depth of anaesthesia are poorly sensitive and specific*. Outside the operating room, this clinical evaluation should consider the effects of sedative drugs, which can markedly influence neurological responses. Although numerous technologies for monitoring the brain are currently available to the anaesthesiologist and ICU physician, dedicated monitoring of cerebral function is still much less frequently applied than, for instance, the close tracking of a wide range of haemodynamic parameters, even though adverse cerebral outcomes are well recognised complications of a variety of surgical procedures, anaesthesia and ICU stays. Among the invasive neuromonitoring techniques in current use, ICP and $SjvO_2$ monitoring systems are the most common. Other invasive methods include $PbtO_2$. Noninvasive techniques for monitoring the brain include multichannel cEEG, pEEG, brain regional oximetry (rsO_2), somatosensory-evoked potentials (SSEPs), and imaging techniques such as transcranial and eye echography, TCDU, pupillometry, CT, MRI and angiography. The CBF can be accurately measured by cerebral CT, direct angiography or PET. Alternatively, CBF and CBF autoregulation integrity can be assessed indirectly by TCDU, which measures blood flow velocity in the cerebral arteries. Undoubtedly, the benefit of the various monitoring tools for guiding treatment and inform on prognosis depends on the underlying disease, but multimodal neuromonitoring is gaining popularity in guiding clinical decision-making.[214]

Electroencephalogram monitoring in the operating room and in the intensive care unit

The EEG effects of anaesthetic drugs were first described by Gibbs *et al.* in 1937,[215] but the use of EEG monitoring during anaesthesia only started once pEEG-based monitors, incorporating dimensionless scales of anaesthetic effects, became available at the end of the 20th Century.[216] Indeed, over decades, in assessing the depth of general anaesthesia, anaesthesiologists had been following the 'Leonardo da Vinci anaesthetic paradigm'

Fig. 5 Does monitoring the brain in the operating room and in the intensive care help keeping it healthy?.



CA, cerebral autoregulation; cEEG, continuous electroencephalography; CPP, cerebral perfusion pressure; CT, computed tomography; EEG, electroencephalogram; ICP, intracranial pressure; NIRS, near infrared spectroscopy; OR, operating room; $PbtO_2$, brain tissue oxygen monitoring; pEEG, processed electroencephalogram; PND, postoperative neurocognitive disorder; POD, postoperative delirium; rsO_2, brain regional oximetry; $SjvO_2$, jugular venous bulb oxygen saturation; TCDU, transcranial Doppler ultrasonography.

after his statement that 'tears come from the heart and not from the brain'.[217] Indeed, they had been monitoring surrogate parameters like heart rate and blood pressure, thereby omitting to look at the functioning brain, which is the primary target organ of anaesthetic drugs effects. Those pEEG-derived monitors, mainly providing a dimensionless index of anaesthetic drug effect on the brain and calculated according to proprietary mathematical algorithms, constituted the first window into brain function monitoring during anaesthesia.[216] *Nowadays, guiding anaesthetic agent administration using those indices is known to reduce the incidence of intraoperative awareness*

with postoperative explicit recall, decrease the intraoperative consumption of anaesthetic agents, shorten time to emergence after the procedure, and decrease length of stay in the post-anaesthesia care unit.[176,218] However, the use of those indices has several limitations, mainly because they were empirically developed, without correlation to a physiological reality, and because their interpretation is impeded by several confounding factors.[172] The current tendency is to promote their use in combination with a reading of the raw EEG tracing, as well as with the reading of a graphic representation of the evolution of the spectral composition of the EEG over time, with recognition of anaesthetic drugs' specific EEG fingerprints.[219] Compared with the single use of indices, this allows a more accurate interpretation of the index value, detection of artefacts and avoidance of excessively deep anaesthesia. In our opinion, the basic knowledge needed to adequately use EEG monitoring during anaesthesia should include the ability to recognize δ, θ, α, β and γ waves, to recognise superimposed oscillations (e.g. α–δ pattern) and burst-suppression patterns, to adjust voltage and power scales to age or other factors affecting the signal, to identify the dynamic changes of the EEG during a gradual increase of anaesthetic agents' concentration, to recognise each anaesthetic agent's fingerprint in relation with main mechanism and neural sites of action, to recognise the effects of nociceptive stimulation on the EEG (β arousal, paradoxical δ arousal or α drop-out), and to identify the patterns observed during emergence from anaesthesia and predicting POD. Indeed, a recent survey showed a lack of anaesthesiologists' knowledge regarding these different aspects: 23% of responders were unsure of the value of the EEG-based monitors.[220] Proper use of those tools and skill improvements might result from guidance obtained from decision-making algorithms (e.g. the Duke Anesthesiology Dreamer),[221] and web-based platforms may be used to improve skills on peri-operative interpretation of the EEG (e.g. www.icetap.org; https://eegforanesthesia.iars.org/).

In the ICU, cEEG monitoring may be used to guide treatment in status epilepticus patients, to detect spreading depolarisation events,[222] and to guide depth of sedation in patients with refractory intracranial hypertension. *In comatose patients after cardiac arrest, it permits reliable prognostication in about 50% of patients, both for a good or poor outcome.*[223,224] *Indeed, a cEEG pattern (i.e., without any flat EEG periods) within 12 to 24 h after arrest is associated with a good neurological outcome,*[225] *while a burst-suppression pattern with identical bursts at any time,*[226] *or persistent suppression or generalised periodic discharges on a flat background at 24 h after arrest is associated with a poor neurological outcome.*[226] *The treatment of most rhythmic and periodic patterns does not improve neurological outcome.*[227] *The prognostic value of the EEG in this case is not influenced by hypothermia or sedation.*[228,229]

Oxygen transport, haemodynamic and brain metabolism monitoring

Multimodal invasive and noninvasive brain monitoring-guided therapy is currently thought a promising attitude to improve the outcome of brain-injured patients, particularly after a traumatic brain injury.[214] Sophisticated methods now allow setting up individualised management, taking account of indicators of cerebral autoregulation to guide CPP targets,[231] $PbtO_2$,[230] NIRS[16] or microdialysis.[231] Studies are ongoing to demonstrate the beneficial effects of those therapeutic choices.[232]

The direct intraoperative monitoring of brain haemodynamic and metabolism is not easily achievable. Local measurements can be made with cerebral microdialysis or $PbtO_2$ catheters, but these methods are invasive and seldomly available during surgery. However, one can infer the adequacy of oxygen transport, brain haemodynamic and metabolism through established intraoperative tests and monitoring. For instance, neurological tests, such as those conducted during awake craniotomies, provide valuable insights.[233] Additionally, intraoperative neurophysiological monitoring using motor-evoked and SSEPs can help assessing the integrity of involved neural structures. For a more comprehensive intraoperative assessment, anaesthesiologists often rely on easy-to use and noninvasive monitors like NIRS, pEEG, raw EEG, TCDU and $SjvO_2$ – or a combination thereof. Those monitors are employed to ensure the optimisation of brain haemodynamic status and metabolism. Assessing their utility at improving brain health and neurocognitive outcome first necessitates a consistent definition of outcome measures, *which has been done by the American Society of Anesthesiologists Brain Health Initiative.*[234] *In current literature, the primary neurocognitive outcomes of interest include POD, PND and mortality*. POD is identified using the established DSM-5 criteria, primarily covering disturbances in attention and cognition that manifest within days after surgery. It appears that pEEG-guided intraoperative interventions to reduce the occurrence of burst-suppression episodes may decrease the incidence of POD,[150,171,235,236] but the supporting evidence is limited because of variance in used monitoring devices, studied populations and considered outcome measures. While there is also a suggestion that pEEG-guided procedures could reduce the occurrence of PND, the effect is small with a large confidence interval.[150,171,235] Further, this conclusion is heavily influenced by only a handful of trials, and pEEG usage does not appear to affect mortality rates.[237] The effect of NIRS-guided intraoperative interventions on short-term postoperative neurocognitive disorders are uncertain.[238] This conclusion is drawn from studies with potential biases, including varying reported results and potential influence from manufacturer sponsorship. Although NIRS might aid in reducing PND incidence, the evidence is weak, mainly because of varying PND definitions and treatment methodologies

in different studies.[235,238–241] Lastly, using NIRS does not seem to impact postoperative mortality rates.[238] In summary, while pEEG and NIRS may potentially help reducing the risk of POD and PND, the level of evidence ranges from low to moderate. There's a pressing need for better designed randomised controlled trials with consistent methodologies, clearly defined study populations, standardised treatment algorithms and larger sample groups. Consequently, and according to current knowledge, intraoperative monitoring alone does not enhance brain health regarding the risk on cognition. It is the actions informed by these devices that may benefit brain health. For an effective intraoperative monitoring, monitors should offer insights into the patient's physiology, should be used on the right patient group by properly trained practitioners, and should prompt actions according to a proper treatment algorithm.

How to keep the anaesthesia and intensive care unit caregivers' brain healthy

A graphical abstract of the key points delivered in this part is provided in Fig. 6.

Burn-out among anaesthesia and intensive care unit caregivers: a real problem?

Maslach *et al.*[242] defined burnout in 1996 as an increased level of emotional exhaustion and depersonalisation, with low levels of personal accomplishment in association with one's job.[2] *It has been included in the 11th revision of the International Classification of Diseases as a syndrome resulting from chronic workplace stress with three dimensions: feelings of energy depletion or exhaustion; increased mental distance form one's job or feelings of negativism or cynicism related to one's job; and reduced professional efficacy.*[243]

Burn-out is more frequent in physicians as compared with the general population, with an increasing prevalence of physicians reporting at least one burn-out symptom.[244] The field of anaesthesiology and intensive care demands a distinctive blend of intellectual abilities and physical dexterity, necessitating attention to detail and swift decision-making, particularly during critical situations. Although this combination of skills is rewarding, it represents a hard challenge, notably when confronted to extended night shifts and long work hours. Notably, a paramount amount of those night shifts is undertaken by trainees across Europe. Anaesthesiology is a field involving the care of acutely ill patients, high productive pressure, work compression and probable perioperative catastrophes.[245] Depending on studies, burn-out symptoms are present in 20 to 50% of anaesthesiologists, which is comparable to the frequency in surgeons or other medical specialties. In most studies, critical care and emergency physicians have the highest rate of burn-out symptoms (up to 55%). In hospital faculty staff, the incidence of severe burnout symptoms is as high as 40%.[244]

The risk factors associated with burnout are work stressors, bad ambiance at work and personal factors. Stress-related factors at work include complexity of clinical tasks, fear of harming the patient, work overload and production pressure, as well as high clinical responsibilities. Anaesthesiologists carry high responsibilities during surgery and may frequently face stressful scenarios, such as the management of an unanticipated difficult airway, cardiac arrest and other life-threatening emergencies. Moreover, the work pattern, at least for larger hospitals, may also be perceived as more stressful because of the high number of on-calls and night shifts, and the higher possibility of working during weekends and festivities, dictating an imbalance between personal and professional lives.[246] Aggravating factors are poor relationships between team members (anaesthesiologists and surgeons), poor working conditions and lack of time. Problems in personal life outside work are major risk factors for burnout. Contrarily, high rewarding and consideration are protective. A perceived effective and respected leadership is also protective.

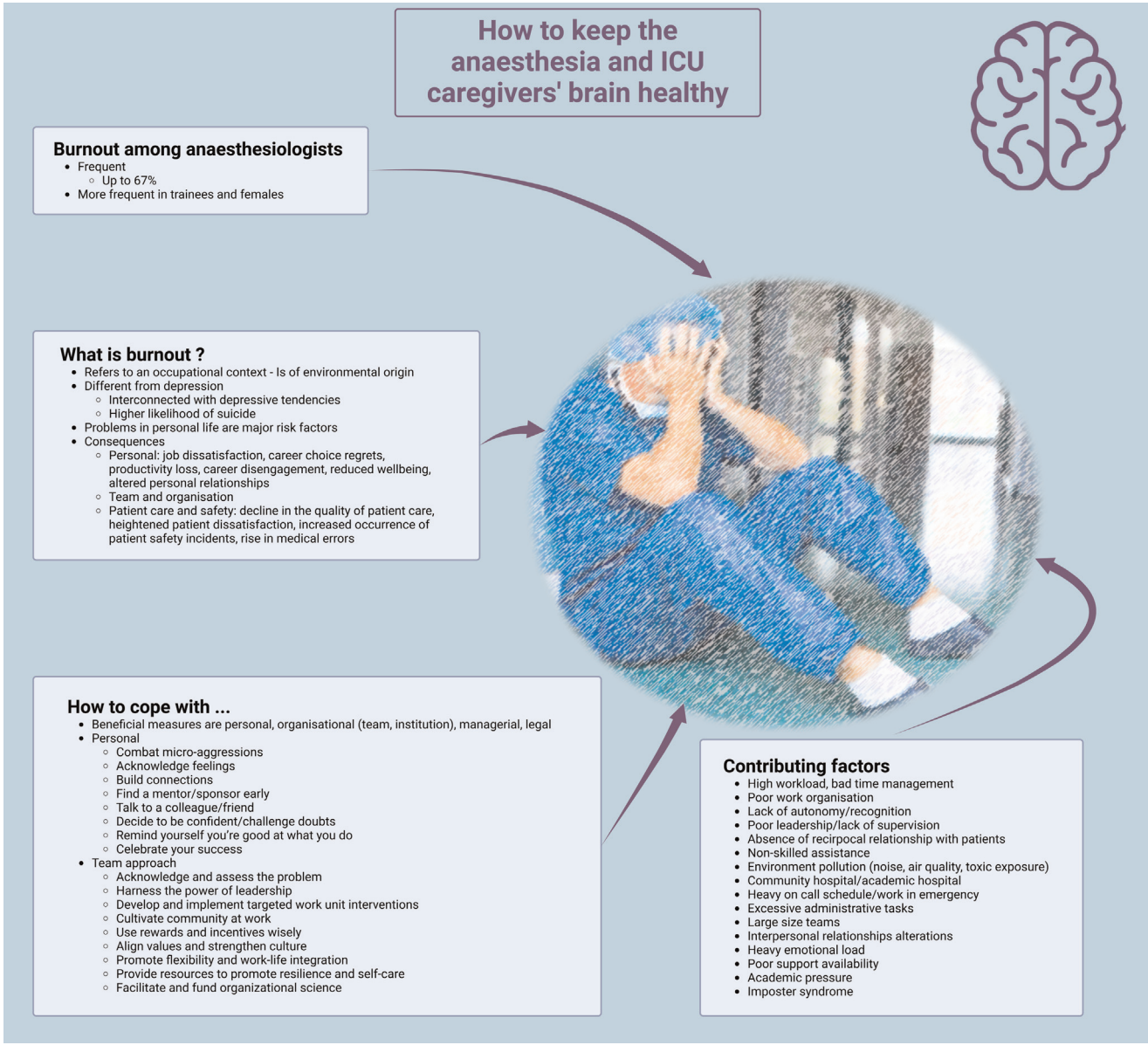
The consequences of burnout are numerous. There exists an intrinsic connection between physician wellness, resiliency and excellent patient care. A recent cross-sectional study suggests that burnout is associated with suicidal ideation in physicians before, but not after, adjusting for depression, and that depression is associated with suicidal ideation after adjustment for burnout. Occupational burnout also has important health implications and is associated with increases in insomnia, mental illness symptoms, headaches, severe injury, type 2 diabetes, extended fatigue, coronary heart disease, gastrointestinal and respiratory concerns, myocardial infarction, atrial fibrillation, musculoskeletal discomfort and all-cause mortality.[246] From the organisational point of view, burnout has also consequences such as overuse of resources and thereby increased costs of care, reduced health outcomes, reduced productivity and sick leave.[247] Burnout is associated with poor quality of patient care, patient dissatisfaction and patient safety incidents. *Fatigue and working time exceeding safety limits are associated with medical errors.*[246,248] *Notably, team performance is a better patient prognostic factor than the ASA physical status.*[249]

Burnout among trainees in anaesthesiology

Anaesthesiology trainees are at special risk of suffering from burnout for several specific reasons.

The first reason is fatigue, to which trainees are more exposed than staff anaesthesiologists.[250] As tiredness takes hold, job performance tends to falter. Consequently, work-related fatigue looms as a pressing issue, profoundly affecting the well being of trainees and the safety of patients. Ramifications of fatigue on patient safety are substantial, potentially leading to a cascade of clinical errors such as medication mix-ups, dosage inaccuracies, catheter misplacements, labelling errors and

Fig. 6 How to keep the anaesthesia and intensive care unit caregivers' brain healthy.



ICU, intensive care unit.

documentation mistakes. Beyond patient safety, the adverse effects of fatigue extend to trainees' ability to manage their duties, projects, personal relationships and mental health. *This is underscored by the average World Health Organisation-5 (WHO-5) well being scores reported by trainees, which suggest a considerable deficit in well being among them.*[251]

Secondly, lack of experience is a risk factor for the development of an imposter syndrome in anaesthesia trainees, as shown in a recent survey distributed through the ESAIC.[252] This is a consequence of patient and other colleagues' expectations that are perceived by trainees. Patients show signs of preference for anaesthesiologists exuding confidence (including the externalisation of a confident and open body language), as they perceive these traits to reflect an ability for better care of them or their family member, and for better leadership.[253] Also, fellow anaesthesiologists aspire to ideal competencies, the ideal anaesthesiologist being the one that is 'striving for excellence' and 'excellent clinical and theoretical skills'.[254]

Thirdly, trainees more frequently receive bullying from their surroundings, including from staff consultants and from other trainees. Bullying may take the form, for

example, of information withholding, which affects performance, of being ordered to do work below his/her level of competence, or of having his/her opinions ignored among others.[255]

The solutions to avoid burnout

Mistakenly, most hospitals, medical centres and practice groups operate under the framework that burnout and professional satisfaction are solely the responsibility of the individual physician. This frequently results in organisations pursuing a narrow list of 'solutions' that are unlikely to result in meaningful progress (e.g. stress management workshops and individual training in mindfulness/resilience).[256] Traditionally, anaesthesiologists have more confidence in their own personal capabilities and physical and intellectual resources to cope with burdens and demands than they have in their workplace resources or their social support from colleagues or superiors.[257] *In this line, the Accreditation Council for Graduate Medical Education recommends the inclusion of self-care measures in common programmes.*[245] At the individual level, coping mechanisms might be useful to avoid the imposter phenomenon and burnout.[258] Coping mechanisms include combatting micro-aggressions, acknowledging one's feelings, building connections, early finding of a mentor/sponsor, talking to colleagues/friends, deciding to be confident/challenging one's doubts and celebrating one's success. In addition, combatting fatigue, and having a comprehensive and multilevel approach is imperative, encompassing personal strategies, team dynamics and organisational reforms. *Studies offer compelling evidence that shorter work schedules for trainees can enhance sleep quality and significantly reduce errors arising from lapses in attention.*[259,260] Many trainees grapple with workloads that render adequate sleep nearly impossible. Encouraging regular, short night breaks for brief naps, providing proper rest facilities during and after night shifts and fostering a shift in culture regarding fatigue acceptance should be a priority.[261,262] Embracing a holistic approach that encompasses personal awareness, team dynamics and organisational changes is vital. At a broader, European level, aligning healthcare practices with the fatigue risk management standards observed in high-hazard industries is paramount.[263] Organisational and team key drivers can be identified as responsible for or being preventive of the development of burnout. Based on their analysis, several organisational strategies can be implemented[256]; acknowledge and assess the problem, harness the power of leadership, develop and implement targeted work unit interventions, cultivate community at work and use rewards and incentives wisely, align values and strengthen culture, promote flexibility and work–life integration, provide resources to promote resilience and self-care, and facilitate and fund organisational science. Local team strategies to improve communication skills to manage conflicts, such as 'Speak up' meetings, and improving team culture to address conflicts grounded on curiosity, respect and transparency may be beneficial,[264] as well as integrating behaviours to sustain psychological health and care excellence within the working units.[265]

Conclusion

The burnout origin is not individual, but environmental. It has individual, team and organisational consequences, and at the end, patients suffer the healthcare burnout impact. Fatigue needs a holistic approach to improve physician wellness and patient safety. Keeping anaesthesia and ICU caregivers' brain healthy needs strategies at several levels that may be implemented in a structured manner.

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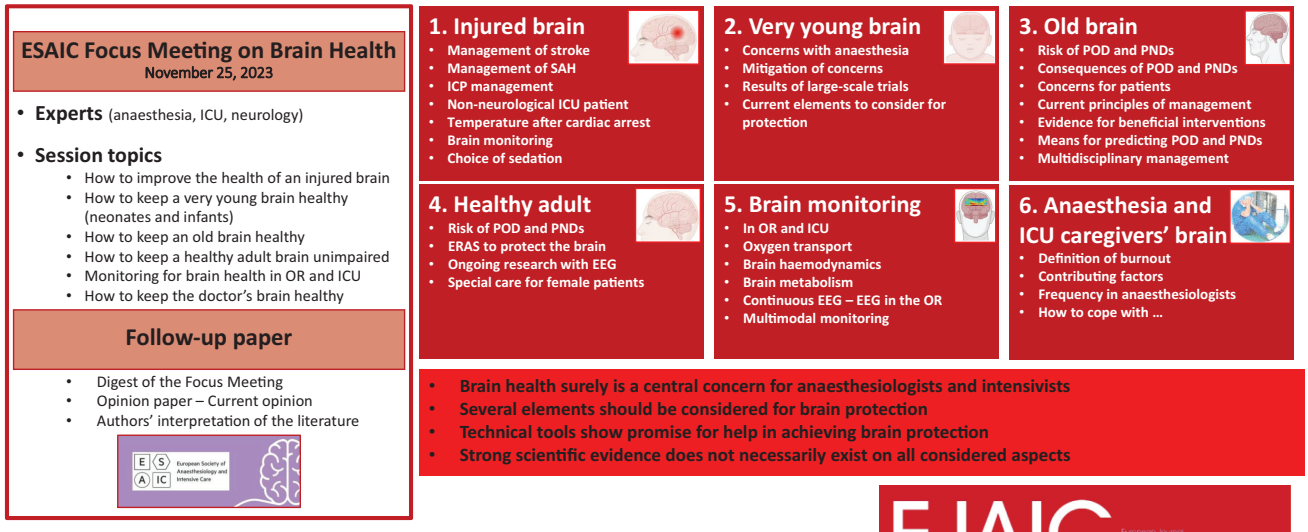
VISUAL ABSTRACT

Brain health: a concern for anaesthesiologists and intensivists



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