Pain is a subjective symptom that, under normal circumstances, triggers a predictable set of objective signs, such as facial grimacing and increased heart rate. Because pain is a warning signal of imminent or ongoing tissue injury, its behavioural manifestations signal to caregivers the need for urgent attention (1). However, in a critically ill infant, the typical signs of pain may be subtle or absent. Their identification and measurement based on observations of behavioural or nonspecific physiological signals remain limited. The difficult task of identifying and decoding the infantile form of self-report is complicated by the fact that the nature of the behavioural signals may vary across the developmental stages of infancy (1,2). Furthermore, in critically ill infants, their fragile and immature state may lessen their capability to organize and exhibit perceived pain as a recognizable response.

Consequently, clinical researchers have explored the use of associated signals to identify pain. As the use of monitoring and neuroimaging techniques becomes more common in pain research, an understanding of these specialized technologies is important. Near-infrared spectroscopy (NIRS) is a noninvasive technique for monitoring tissue hemodynamics and oxygenation. There are indications that NIRS is capable of detecting the cerebral hemodynamic changes associated with sensory stimuli, including pain, in infants. These developments suggest that NIRS may play an important role in research focusing on pain perception in critically ill infants. The present review briefly describes the cortical responses to noxious stimuli, which parallel cerebral hemodynamic responses to various stimuli. This is followed by an overview of NIRS technology including a summary of the literature on functional studies that have used NIRS in infants. Current NIRS techniques have well-recognized limitations that must be considered carefully during the measurement and interpretation of the signals. Nonetheless, until more advanced NIRS techniques emerge, the current devices have strengths that should be exploited.

Key Words: Infants; Near-infrared spectroscopy; Neurodiagnostic technique; Nociception; Pain

La spectroscopie proche infrarouge du cerveau pour mesurer l’activité évoquée par une stimulation nociceptive chez des nourrissons gravement malades

Les signes de douleur peuvent être discrets ou inexistants chez le nourrisson gravement malade. La nature complexe de la douleur peut en compliquer davantage la détermination et la mesure. Puisque les techniques de surveillance et de neuro-imagerie sont davantage utilisées dans le domaine de la recherche sur la douleur, il est important de comprendre ces technologies spécialisées. La spectroscopie proche infrarouge (SPIR) est une technique non invasive pour surveiller l’hémodynamique et l’oxygénation des tissus. Selon certaines indications, la SPIR peut permettre de décoder les modifications hémodynamiques du cerveau associées aux stimuli sensoriels, y compris la douleur, chez les nourrissons. Selon ces observations, la SPIR pourrait jouer un rôle important dans la recherche axée sur la perception de la douleur chez les nourrissons gravement malades. La présente analyse contient une brève description des réponses corticales aux stimuli nuisibles, parallèles aux réponses de l’hémodynamique cérébrale à divers stimuli. Ces constats sont suivis d’un aperçu de la technologie de la SPIR, y compris un sommaire des publications sur les études fonctionnelles qui ont fait appel à la SPIR chez les nourrissons. Les techniques de SPIR actuelles comportent des limites bien connues, qu’il faut évaluer soigneusement lors de la mesure et de l’interprétation des signaux. Néanmoins, tant que des techniques de SPIR plus avancées n’auront pas émergé, les appareils existants comportent des qualités qu’on devrait exploiter.

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to the bedside, which enables continuous signal recording capable of capturing responses to intermittent stimuli. It would appear that there are new and exciting avenues for the assessment of nociception that may be more sensitive and, perhaps, more specific to the pain response for populations such as premature and term infants or critically ill children.

Additional studies are necessary to determine the feasibility, usefulness, specificity, sensitivity and, perhaps most importantly, the clinical significance of these novel physiological assessment instruments in different painful conditions. Among other opportunities, this would provide possibilities for establishing the psychometric properties of currently available pain assessment instruments not requiring specialized equipment in critically ill infants. Not only would noninvasive monitoring techniques, such as NIRS, detect pain perception and the respective cortical regions involved in this experience, they may also enable the identification of the most accurate or sensitive observational pain indicators in specific situations (11,19). To date, only one published study has examined the relationship between NIRS with both physiological and behavioural indicators (ie, three facial expressions) from a pain assessment instrument in a population of newborn infants; moderate associations were demonstrated among these variables (11).

In the present article, we briefly describe the cortical responses to noxious stimuli, followed by an overview of NIRS technology and, finally, a literature review of functional activation studies using NIRS in critically ill infants, with a particular emphasis on pain activation studies. The objective is to provide the reader with a better understanding of the technology, its applications in pain research and its potential use in clinical settings.

CORTICAL PAIN RESPONSES

The brain is the principal processor of internal and external sensory experiences including pain. It receives messages, relays them to the appropriate areas for interpretation and, subsequently, transforms them into appropriate responses (20). Many aspects of the pain experience can be studied including peripheral nociception, central processing, cortical modulation, and cognitive-emotional and psychological qualities. Our understanding of the pain experience has increased through the identification of specific cerebral regions involved in pain processing. It is well established that specific regions implicated in pain processing are located deeper in the brain than others (ie, insula and anterior cingulate cortex) and that to be examined, advanced neuroimaging techniques with high spatial resolution, such as MRI, are required (17,18). Conversely, the primary somatosensory cortex, which is involved in the processing of sensory input, is located more superficially; activity in this cortical region is more accessible to examination by noninvasive optical techniques such as NIRS.

Cortical activation and pain processing

Emotional and motivational processing at higher cortical levels are necessary for an individual to fully experience pain (21). More primal physiological reactions, such as limb withdrawal and an increase in heart rate, are the result of subcortical level responses of the nervous system, ie, spinal cord, brainstem, hypothalamus and thalamus (22). Behaviours such as facial actions and cry are valued as good proxy physiological reactions, such as limb withdrawal and an increase in heart rate, are the result of subcortical level responses of the nervous system, ie, spinal cord, brainstem, hypothalamus and thalamus (22). Behaviours such as facial actions and cry are valued as good proxy physiological reactions, such as limb withdrawal and an increase in heart rate, are the result of subcortical level responses of the nervous system, ie, spinal cord, brainstem, hypothalamus and thalamus (22). Behaviours such as facial actions and cry are valued as good proxy

This is the case for both [HbO2] and [HbH] increases. This phenomenon has been tentatively explained by anatomical differences in cerebral neuronal networking in immature regions of the brain. For example, compared with older children (older than six years of age) and adults, there is a higher number of synaptic connections in the immature visual system (30). Thus, cerebral neurovascular coupling could differ in young children compared with more mature neuronal networks found in adults (31).

During baseline brain metabolism, an equilibrium between oxygen use and blood flow is present. Consequently, the cerebral oxygen extraction fraction (OEF), which can be described as “the percentage of the oxygen delivered to the brain that is utilized by the brain” (32), is very stable and can be used as a reliable indicator to define brain metabolism. In the awake resting state, brain energy requirements are quite high, accounting for approximately 20% of the oxygen and glucose use in the whole body, and 10% of the cardiac output (33). During brain ‘activation’, there is a modest mobilization of energy (ie, approximately a 10% increase from baseline activity) characterized by increases in blood flow, glucose use and oxygen delivery. However, the increase in oxygen use is slightly lower than the increase in oxygen delivery, resulting in a relative decrease in OEF because the supply transiently exceeds the demand, reflected by an increase in [HbO2] and a decrease in [HbH]. In comparison, a ‘deactivation’ relates to a transient increase in OEF and represents a decrease in neural activity compared with baseline metabolism, but not all decreases are deactivations (26,32).

These neurovascular and neurometabolic coupling mechanisms support the use of techniques that measure regional cerebral hemodynamic responses to increase our understanding of pain processing at the cortical level. The following section provides a description of NIRS, which is a noninvasive bedside technique for monitoring

Ranger et al

Pain Res Manage Vol 16 No 5 September/October 2011
cerebral perfusion and oxygenation. An overview of functional NIRS (fNIRS) research articles within the infant population is also featured, with a particular focus on pain and NIRS studies.

NIRS

NIRS is an optical technique based on the principle that light in the near-infrared (NIR) range (700 nm to 1000 nm) is able to pass through soft tissue and bone with relative ease, and can penetrate brain tissue to a depth of up to 8 cm (34,35). The depth of penetration of the NIR light is dependent on the thickness and density of the tissue. Accordingly, when illuminating the somatosensory cortex area of the premature infant, the light may enter much deeper, with signals penetrating the primary somatosensory cortex and parts of the secondary somatosensory cortex, insula, cingulate cortex, thalamus and amygdala (34). Due to the thickness of adult skulls, light does not penetrate more than 5 cm from the surface. The light is mainly absorbed by two chromophores: hemoglobin and cytochrome aa3. A chromophore is a substance that absorbs light of a given wavelength (eg, NIR light spectrum varies between approximately 650 nm and 1000 nm), and those found in living tissues are HbO2, HbH and cytochrome oxidase (36). Each of these chromophores has its peak NIR light absorption at a specific distinct wavelength.

The calculation of the chromophore’s concentration and absorbance of NIR light in the tissue is made possible by a modified Beer-Lambert law (37). This law permits the calculation of the attenuation of a light source that passes through a given substance. When light penetrates a medium that is not homogeneous, such as living tissue, it does not simply travel from the source to the receiver – part of its propagation is scattered and lost. Thus, the distance from the light source to the receiving end is affected by a differential pathlength factor (DPF). The DPF has been calculated for various biological tissues, but has also been shown to vary between participants, which may partly explain the complexity in standardizing NIRS variables across participants (35,37).

The hemodynamic signal obtained with the NIRS technique is based on the absorption of NIR light by hemoglobin, which in turn, depends on the oxygenation state of hemoglobin circulating through the tissues. Thus, NIRS measures the relative change in the tissue concentration of intravascular HbO2 and HbH (34-36).

Cerebral hemodynamics and NIRS

Research using NIRS to study variations in cerebral oxygenation and hemodynamics of human neonates originated in the work by Brazys et al in 1985 (38). Although there have been significant advances in this field during the past decade, the understanding of how blood flow, metabolism and neuronal activity interact to affect the NIRS signals remains incomplete (34). Establishing the validity of the NIRS measures has also been difficult because few alternative technologies exist to serve as a ‘gold standard’ (35).

The study of hemodynamic changes to assess the functional activation in the brain is based on the assumption that a given stimulus will induce a neuronal response, which in turn, triggers local vasodilatation, with an increase in cerebral blood volume (CBV) and cerebral blood flow (CBF) (36). Using NIRS, we are able to infer changes in cerebral blood flow by measuring changes in the hemoglobin difference, which is obtained by calculating the difference between the changes in [HbO2] and [HbH]. As for changes in CBV, they largely reflect the changes in total concentration of hemoglobin or ‘total hemoglobin’ ([HbT]), which is the sum of [HbO2] and [HbH] (39,40). Under these circumstances, an increase in the relative concentration of the [HbO2]/[HbT] ratio suggests that CBF has increased in excess of oxygen consumption, which is what is expected to happen during a noxious stimulus. This principle illustrates how neural inputs may provoke hemodynamic changes in the cortical area where the ‘message’ is processed. On the other hand, a decrease in the relative [HbO2] and [HbT] compared with a baseline measure can be interpreted as a regional cortical deactivation (34,41-44) (Table 1). Such observations have been described in a study of hemodynamic changes in the olfactory cortex following ‘strong odours’ stimulation (ie, disinfectant or tape remover substances) in premature infants (45).

Clinical application and fNIRS studies

NIRS has been providing quantitative data regarding the oxygenation status of living biological tissue since the pioneering work of Jobris (46) in the late 1970s. During the past two decades, studies have been conducted to assess the feasibility of this technique for monitoring variations in cerebral oxygenation of patients at risk for brain damage (34,36). NIRS studies can be divided into two categories: measurement of brain activity through assessment of dynamic relative changes in regional cerebral blood flow in real time (continuous wave-type instrument); and imaging of brain activity as a function of time (time-resolved instrument) (47). For additional references about these NIRS techniques, refer to the article by Hoshi (47).

Many advantages of this optical technique have been described. Specifically, it is a safe, noninvasive, bedside technique for exploring pathophysiological mechanisms underlying brain injury in sick infants (48). It has enormous potential as a tool for measuring cerebral hemodynamic responses to a variety of stimuli including changes in blood pressure, oxygenation, carbon dioxide and neuronal activation. The excellent temporal resolution of NIRS makes it a potentially valuable tool for assessing various pathologies and their management. It can be adapted to many experimental and clinical situations, and combined with other electrophysiological and neuroimaging techniques (34,36,40). Currently, it is a clinical and research tool providing anesthesiologists, neurologists, neurosurgeons, physiologists, cardiac surgeons, neonatologists and nurses with important insights into the hemodynamic and oxygenation activity of the brain in adults and children (36). NIRS has been used in studies of brain neurophysiological development and reactivity in preterm and term infants (12,35,36,49-51), as well as in intra- and postoperative cardiac infant studies (52-54). Regarding this last area, NIRS technology has assisted researchers in determining the complex changes in cerebral hemodynamics that persist during the early postoperative period. As such, these ongoing cerebral hemodynamic disturbances may impact cerebral hemodynamic-activation coupling (36), thereby confounding the interpretation of cortical activation by noxious stimuli. Furthermore, certain treatments provided to critically ill infants may have significant effects on cerebral circulation such as surfactant administration, mechanical ventilation, blood transfusion, surgery, hypothermia, analgesics/sedatives, caffeine and indomethacin therapies (34,35,55-57). The effects of these agents on NIRS measurements need to be considered carefully during studies in this complex clinical scenario.

In the past decade, there has been an increase in brain functional activation studies in the newborn evaluating cortical activation to certain stimuli using NIRS technology such as olfactory (45,58), visual (29,59), auditory (34), tactile and pain stimulation (9-11). Brain functional activation studies have opened the door to a whole new area of research. These studies have already provided valuable insights into the functional topography of the different components of the sensory

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| Table 1 | Summary of hemodynamic measures derived from near-infrared spectroscopy data |
|---------------------------------|---------------------------------|
| Name                           | Formula                         |
| Total hemoglobin (Δ[HbT])       | Δ[HbO2] + Δ[HbH]                |
| Hemoglobin difference (Δ[HbD])  | Δ[HbO2] – Δ[HbH]                |
| Cerebral blood flow (ΔCBF)      | Δ[HbO2] – Δ[HbH] = Δ[HbD] ≡ ΔCBF |
| Cerebral blood volume (ΔCBV)    | Δ[HbO2] + Δ[HbH] + Δ[HbT] ≡ ΔCBV |
| Principle                       | If [HbO2] – CBF > O2 consumption |

Data measured by the near-infrared spectroscopy technique represent relative changes in the oxygenation state of the hemoglobin (Δ). Data from references 39, 63, 65 and 66.
system, and this is likely to remain an important approach for future research. Bartocci et al (9), for example, demonstrated that a noxious (ie, venipuncture) stimulus on the hand induced a significant [HbO2] increase in the contralateral somatosensory cortex of preterm infants. Because there was no accompanying change in the occipital cortex, this argued against a global, sympathetically mediated response as might be occurring after sudden changes in blood pressure in infants with tenuous cerebral pressure autoregulation, or after a general state change response to pain (50).

Currently, multichannel NIRS devices that can cover multiple regions of the scalp are not readily available, but their application in experimental contexts is increasing in adult and pediatric NIRS research (47,60,61). Recently, researchers using diffuse optical tomography (a multichannel NIRS device) were able to demonstrate a specific pain signal response in the somatosensory cortex of healthy adults after a noxious thermal stimulation (61). As these techniques continue to advance, obstacles to their application in younger, less healthy populations will likely be reduced. Multichannel NIRS devices bring increasing spatial resolution to the already excellent temporal resolution of NIRS, enabling better functional mapping and providing more insight into brain function (47). For a comprehensive review of the progress and state of NIRS instrumentation and their clinical applications in preterm and term neonates, we invite readers to refer to Wolff and Greisen (48).

NIRS and pain research in critically ill infants

The literature examining pain and brain functional activation studies in critically ill infants is relatively recent. To date, only three studies reporting on pain and NIRS have been published (9-11), all of which involved preterm and term neonates.

Slater et al (10) were the first to report somatosensory cortical activation following heel lance in a group of 18 newborns who were 25 to 45 weeks’ postmenstrual age (each newborn was studied one to five times). They demonstrated a clear distinction between spinal and cortical processing, where strong reflex reactions (ie, spinal) did not automatically correspond to more perceived pain (ie, cortical), as demonstrated with nonsignificant changes in the cerebral total hemoglobin concentration. Notably, these cortical activations were shown to be discriminative to pain because Von Frey hair stimulation (ie, filaments used to measure the threshold for touch-evoked sensation) of the plantar surface of the foot caused a flexion withdrawal response but did not lead to a cortical activation. Thus, spinal reactions could serve as protective reflexes.

Increases in [HbT] in the contralateral somatosensory cortex were found following heel lance in infants as young as 23 weeks of age (mean ± SD [HbT] increase of 7.74±1.10 μmol/L) and were independent of global hemodynamic changes. Finally, the increases in [HbT] depended on the gestational age, very few data were provided in the three studies conducted to date regarding systemic physiological responses, which are important factors to consider when measuring cerebral hemodynamic responses to noxious stimuli. Only two studies (9,11) provided data regarding heart rate and peripheral arterial blood oxygen saturation compared with cerebral oxygenated and [HbT] changes. Most importantly, none of the studies provided data related to blood pressure, which is known to be related to CBF and CBV changes during nociceptive events in sick infants (12,63). Advances in this field will depend on the careful measurement and analysis of other simultaneous physiological changes that may confound the interpretation. In addition to factors that have been found to be associated with cerebral hemodynamic changes (ie, gestational age, sex, asleep/awake state), important confounders such as sound and lighting in the neonatal intensive care unit, as well as infants’ severity of illness remain unexplored, but should be accounted for in future studies.

Limitations of the NIRS technique

NIRS technology is not without limitations, some of which may be more difficult to overcome than others. The amount of NIR light reaching the detector optode is influenced not only by the concentration of the absorbing chromophores (eg, hemoglobin), but also the amount of photon scattering. With more scattering, the light has a longer path through the tissues and, therefore, has a greater chance of being absorbed. Currently, a major drawback of most available
devices is the unknown path length of the NIR light within tissues. For this reason, it is still necessary to apply a constant DPF to the measurements and to assume that this path length does not change significantly during the course of a study. This remains a tenuous assumption in many clinical situations. Tables of differing pathlength factors in brain tissues for different participants are used, but are known to vary significantly with age (35,37). As such, measured data should be regarded as an absolute change in hemoglobin concentration rather than absolute values (34). Another major drawback of NIRS technology is related to the difficulty in accurately identifying the exact region that is sampled by the NIR light (47). However, conducting multichannel NIRS trials, as mentioned previously, enables a more accurate mapping of cortical areas and improved discrimination (61).

NIRS technology is sensitive to various factors that may confound results. Conditions related to critical illness that may result in metabolic somatosensory changes could confound pain-related activation measurement using NIRS. Environmental stimuli also need to be taken into account when performing NIRS because they can bias the results. Patient movement can cause artefacts and disruptions in data collection. Nonetheless, this technology has the major advantage of enabling continuous bedside monitoring of cerebral activity and hemodynamics in a noninvasive manner, which is particularly valuable for the critically ill infant. Finally, despite the fact that NIRS has some reliability issues limiting its widespread use for clinical monitoring of cerebral hemodynamics, it can provide significant insight into the multifaceted physiological and pathological responses to stimuli (35,61,64). Until more advanced NIRS technologies become available, the strengths of the current devices should be exploited and the limitations carefully considered when interpreting data generated by this unique neurodiagnostic technique.

**CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH**

Although our understanding of the multidimensional experience of pain has advanced over the past century, avenues remain unexplored, particularly in vulnerable populations such as noncommunicative patients. NIRS has potential as a technique for assessing pain-evoked cerebral activation in critically ill infants. Given the complexity of NIRS technology, the paucity of research supporting its use in pain measurement in critically ill infants, and the need for tight control of many confounding factors as well as artefacts, more studies are clearly needed. At this stage, it may be best to consider this neurodiagnostic technique solely as a research tool that will improve our understanding of pain perception, increase the psychometric features of currently available pain assessment instruments and, perhaps, assess the efficacy of pharmacological and nonpharmacological treatments.

Determining what constitutes a clinically significant change in the measured parameters (ie, [HbO2], [HHb] and [HbT]) compared with normal fluctuations that occur in the brain tissue by sampling both healthy and critically ill infants of differing developmental ages is also needed. Finally, because a variety of devices using NIRS technology are currently available for research (eg, NIRO devices, Hamamatsu Photonics, Japan) and clinical use (eg, INVOS Systems, Somanetics, USA), setting standards for specific use in pain measurement could facilitate the generalization of findings.

A major question that is raised by clinicians caring for noncommunicative patients is whether this technique will move beyond research to become a bedside monitoring technique for pain assessment. Moreover, can this technology help us monitor the cerebral hemodynamic changes due to prolonged pain versus acute procedural pain, and can it make this distinction? When considering the research findings and current available devices, this may seem improbable. Nevertheless, this approach should not be abandoned because its usefulness as a portable means to functional brain mapping is evolving well and setbacks are being resolved (47,61). If the NIRS technique is validated over time as an accurate measure of pain, other issues will arise, as with all proxy measures of pain, such as determining successful analgesic response. All pain indicators for noncommunicating people require a series of validation studies with replication, and NIRS would be no exception.

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