ARTICLES

Cerebral Hemodynamic Response to Unpleasant Odors in the Preterm Newborn Measured by Near-Infrared Spectroscopy

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ABSTRACT

Newborn infants in intensive care units are exposed to several unfamiliar smells, mostly related to the nosocomial environment. How the preterm baby perceives these olfactory stimulations remains unclear. Near-infrared spectroscopy can be performed noninvasively above the olfactory cortex to monitor changes of cerebral blood flow as an indicator of cortical activation. The aim of this study was to explore by near-infrared spectroscopy how odorous substances routinely used in the neonatal intensive care unit influence bilateral cortical hemodynamics in the olfactory region of the brains of preterm infants. Specifically, a detergent (Neomidil) and an adhesive remover (Remove) have been tested. Twenty preterm neonates of gestational age 30–37 wk (mean 33.7 ± 2.3 SD) and postconceptional age 32–37.3 wk (mean 35.5 ± 2.75 SD) were monitored by near-infrared spectroscopy. Two optode pairs were placed above the anterior orbitofrontal gyri, which is involved in olfactory processing, on each side of the skull. Fifteen babies were exposed to the smell of a disinfectant and five babies to that of a detergent, both applied to small cotton pads. Changes of oxygenated Hb and deoxygenated Hb were recorded before, during, and after a 10-s stimulus. In 17 out of 20

babies, there was a decrease in oxygenated Hb and total Hb after the exposure to the substances. The decrease was significantly greater in the right side than in the left side. This change was different from that observed in our previous study after exposure to colostrum and the pleasant smell of vanilla, which elicited an increase in blood oxygenation in the same region. The biologic significance of this finding is unknown. We conclude that cortical hemodynamic modifications occur in the preterm newborn after exposure to preparations commonly used in the neonatal intensive care unit. A lateralization seems to occur in processing unpleasant olfactory cues. (*Pediatr Res* 50: 324–330, 2001)

Abbreviations:

NICU, neonatal intensive care unit
NIRS, near-infrared spectroscopy
[Hb O₂], oxygenated Hb
[Hb H], deoxygenated Hb
[Hb tot], total Hb ([Hb O₂] + [Hb H])
r-CBF, regional cerebral blood flow

The newborn infant is exposed to a multitude of nonphysiologic environmental stimuli, which are perceived, processed, and elaborated in the form of different responses, both physiologic and behavioral. Some of these stimuli have been shown

to affect the growth, development, and survival of the neonate, especially the premature infant treated in the NICU (1–5). Most studies have focused on responses to visual (3, 5, 6), auditory (3, 5, 7, 8), and tactile stimulation (1, 3, 5). However, there is little information about the responses to a large variety of pungent and artificial odorous compounds (*i.e.* disinfectants, detergents, adhesive removers) to which the premature baby is exposed. In a recent study by our group, we found that unfamiliar, but likely pleasant, olfactory cues such as colostrum and vanilla can elicit a hemodynamic cortical response in healthy newborns. This suggests olfactory processing (9).

The olfactory system is well structured from 32–34 wk of gestation and distinct behavioral responses to olfactory stimuli

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have been observed from 32 wk of gestation (10). Other components of the olfactory system, such as trigeminal and accessory subsystems, seem to be responsive at 30 wk of gestation or even earlier.

Cortical processing in preterm infants in response to olfactory stimuli, particularly when these are unfamiliar and likely unpleasant, is still unclear. The main aim of the present study was to assess using NIRS the hemodynamic changes in the olfactory cortex when premature infants were exposed to two, likely unpleasant, substances commonly used in the NICU.

NIRS is a noninvasive technique capable of monitoring changes in blood concentration of chromophores such as [Hb O₂] and [Hb H]. Recently, NIRS has been used to study functional activation of various cortical regions of the human brain. The basic assumption is that changes in [Hb O₂] and [Hb H] concentration are strictly related to changes in blood flow, which in turn are coupled to neuronal activity (11–15). Although the majority of studies performed thus far have used adult subjects, this method has also been used on newborns during the last 3 y (6–9). The relationship between hemodynamic changes and neuronal activation in the illuminated cortical area has been studied under various conditions, such as in response to visual (6, 12, 16–19), acoustic (7, 8), and olfactory (9) stimuli.

MATERIAL AND METHODS

Study Group

Twenty preterm newborn infants with a mean gestational age (GA) of 33.7 wk (range, 30–37), a mean postconceptional age (PC) of 35.5 wk (range, 32–37.3), and a mean postnatal age (PN) of 12.5 d (range, 0.75–35) at testing were studied. Of these, 15 were admitted to the NICU, Department of Pediatrics, Gaslini Institute, University of Genoa (mean GA, 33.1 wk; range, 30–36 wk), and 5 to the NICU, Astrid Lindgren's Children's Hospital, Karolinska Institute, Stockholm (mean GA, 35.4 wk; range, 33–37).

At the time of the experiment, all babies were in stable condition and breathing spontaneously without any need of oxygen supplementation or infusion. All were fed with mother's milk, given by bottle, and at least 2 h had passed since their last meal (mean, 2.9 h; range, 2–4 h; SD 0.47). Cranial ultrasound scans were normal in all babies.

The babies were studied in their incubator while lying in the supine position in a quiet, awake state (20). The incubator temperature was kept constant around 29–30°C, the light was dim, and the noise level was reduced as much as possible. The duration between the last handling and the experimental time was at least 30 min. Parents were allowed to be present at the experiment session, but they were asked not to touch or talk to their baby during the test.

The local ethics committees in both Stockholm and Genoa approved the study and parental informed consent was obtained.

Heart Rate Respiration Rate and Arterial Oxygen Saturation Data

Heart rate (HR) respiration rate (RR), and arterial oxygen saturation (Sao₂) were simultaneously registered during the experiment using an HP monitoring system including pulse oximetry (Hewlett-Packard, Boeblingen, Germany). HR, RR, and Sao₂ data were transferred through an RS232 interface card to a personal computer at a sampling rate of 1 Hz. Average values for the baseline period, as well as at 10, 20, and 30 s after the stimulus, were calculated for each infant. Stepwise regression analysis (ANOVA-MANOVA) and Newman-Keuls posthoc comparisons were used to compare the different values throughout the experiment. Differences in the male and female groups were analyzed using a *t* test for independent samples.

Odors

In Genoa, we tested on 15 babies the smell of a disinfectant solution (Neomidil, Pharmec, Rome, Italy) routinely used in our NICU. This solution is composed of benzyl chlorate (0.25%), ethyl alcohol (66.29%), and excipients such as lemon oil, acetone, isopropyl alcohol, camphor, and purified water.

In Stockholm, we monitored five neonates during exposure to the smell of a detergent frequently used to remove tape from an infant's skin (Remove, Smith & Nephew; Mölndal, Sweden). This substance contains dipropylene glycol methyl ether (45–55%), water, and mineral essences.

The study population was originally composed of 30 babies. However, the recordings could not be evaluated in 10 babies because of movement artifacts on the NIRS trace. Most of these artifacts were the result of head movements, which were often related to the baby's reaction to the smell of the tested substance. Of these 10 babies, 3 (2 females and 1 male) were admitted to Genoa Hospital and 7 (4 females and 3 males) to Karolinska Hospital. GA and age at the time of the experiment were similar to those of the study group.

A 2 × 2-cm pad was soaked in 1.5 mL of the testing compound (the remover was presoaked in its commercial package) and thus presented to the infants at a distance of about 2 cm from the nostrils for 10 s. The pad was held by the researcher at the far end so that the fingers were approximately 4 cm from the infant's nostrils. The cotton pad was moved slowly from left to right and vice versa, but essentially remained in front of both nostrils for the entire 10-s duration. Care was taken not to touch the skin of the baby. The infant was not exposed to the tested substance during the hour before the experiment.

Responses to the stimuli were compared with those observed in our previous study (9) after exposure to colostrum as a biologically meaningful odor, vanilla (vanilla essence, 4-hydroxy-3-methoxy-benzaldehyde, The Body Shop, West Sussex, U.K.) as a likely pleasant odor, and water as a negative control.

Panel Evaluation of the Smell

The intensity and hedonic value of Neomidil, Remove, and the three control fluids (distilled water, colostrum, and vanilla),

were evaluated by 12 adults (6 males and 6 females). For rating of intensity, we used a 20-cm long visual analogue scale. For rating of pleasantness, the middle point of the 20-cm scale was defined as neutral, the left extreme (-10 cm) as maximal unpleasantness and the right extreme ($+10$ cm) as maximal pleasantness. The gradation expressed by the panelists as measured in centimeters was analyzed using ANOVA and posthoc testing.

Water and colostrum were presented first, followed by vanilla, disinfectant, and detergent. This sequence was chosen to avoid stronger odors affecting the perception of more faint odors.

A cotton swab soaked in the solution was moved under the nostrils at a distance of 2 cm for 10 s. All the panelists were exposed to the same sample of colostrum. This sample was taken from a mother 2 d after she gave birth to a 37-wk-gestation baby.

NIRS Settings

Changes in $[\text{Hb O}_2]$, $[\text{Hb H}]$, and $[\text{Hb tot}]$ were monitored using a double-channel NIRS device (NIRO 300, Hamamatsu Photonics, Hamamatsu, Japan). This technique allows noninvasive monitoring of concentration changes in natural chromophores, such as Hb in oxygenated and deoxygenated state, as well as cytochrome *c* oxidase—the last enzyme of the respiratory mitochondrial chain—in the redox state of the. Light in the near-infrared spectrum between 700 and 1000 nm can penetrate biologic tissues, including bone. Based upon the modified Beer-Lambert law applied to light attenuation changes through the illuminated tissue, it is possible to calculate changes in chromophore concentration. The basic principles of NIRS and its reliability in studying newborn infants have been described in detail (21–25).

In brief, NIRO 300 is provided with four pulsed-laser diodes producing light at different wavelengths (775, 810, 850, and 910 nm). Each diode has a pulse frequency of approximately 2 kHz, and each pulse lasts about 100 nsec. Near-infrared light is provided by an emission optode $[8 \text{ mm } (\text{O}) \times 4 \text{ mm } (\text{H})]$ and detected by a recipient optode $[20 \text{ mm } (\text{O}) \times 8 \text{ mm } (\text{H})]$ where O = diameter and H = height. The optodes were placed in a special black semirigid rubber holder with an interoptode distance of 4 cm. Each pair of emission and recipient optodes was positioned symmetrically on each side of the skull. The emitting optode was placed 2 cm above the midpoint of the line connecting the external angle of the eye to the homolateral tragus (slightly anterior to the T3 position according to the international EEG 10–20 system) (Fig. 1). This location likely enabled the illumination of the orbitofrontal gyrus of the frontal lobe. We established a differential path-length factor (DPF) of 4.2 (26). Sampling was performed every second.

Smell Stimulus and Data Storing

After placing NIRS optodes on the head, a starting period of about 2 min was passed, during which the signal was adjusted and stabilized. Next, a 30-s period of NIRS baseline was defined. The small pad soaked in the substance to be tested was then moved slowly from one nostril to the other for 10 s at a

Figure 1. Optode position. The sketch shows how the optodes (gray circles; R, receiver; E, emitter) were positioned on the skull of the baby to illuminate the olfactory region. The international standard EEG electrode position has been used as a reference system (white circles) for positioning the optodes. Each pair of optodes was placed symmetrically on both sides of the head. The distance between the E and R was 4 cm. As an anatomical reference, the line connecting the lateral corner of the eye to the tragus was taken. The emitting probe was located approximately 2 cm (± 0.5 cm) above the midpoint of this line.

distance of approximately 2 cm. Through an RS232 A/D board, NIRS data were transferred online to a personal computer. The beginning and end of each registration period were marked on the NIRS curve. The initiation of the 10-s smell exposure period was also marked. Changes in $[\text{Hb O}_2]$ and $[\text{Hb H}]$ were analyzed and $[\text{Hb tot}]$ values were calculated.

Data Analysis and Statistics

For each infant, two 30-s periods were compared (Fig. 2). Period 1 (P1) consisted of a 30-s baseline duration before exposure to the smell. Period 2 (P2) included the exposure time (10 s) and the following 20 s. The data registered by the NIRS apparatus were exported every second. Thus, each of the periods contained 30 numerical values corresponding to $[\text{Hb O}_2]$ and 30 values to $[\text{Hb H}]$. $[\text{Hb tot}]$ was calculated off-line as $[\text{Hb O}_2] + [\text{Hb H}]$ (27). For each baby, the mean value of the difference between P1 and P2 for $[\text{Hb O}_2]_{\text{diff}}$, $[\text{Hb H}]_{\text{diff}}$, and $[\text{Hb tot}]_{\text{diff}}$ were calculated by subtracting P1 values from P2 values.

Figure 2. Different phases of the experiment course (bottom panel) and the corresponding periods that have been chosen for analysis (top panel). The 30-s baseline constitutes Period 1. The 10-s smell exposure time plus 20-s period immediately after the exposure comprise Period 2. This experimental procedure was used when the baby was exposed both to Neomidil and Remove.

For each second of registration, an averaged value was calculated from all 20 babies, both in the basal condition (P1) and after stimulus (P2). In such a way it was possible to derive average curves describing the hemodynamic changes in the left and right hemisphere during the basal condition as well as during and after the exposure. Also, an averaged curve with mean values of $[Hb]_{diff}$ was calculated.

To compare exposure-related changes in the same hemisphere, the P1 and P2 average curves for $[Hb O_2]$, $[Hb H]$, and $[Hb tot]$ were compared for each. To compare the differences between the two hemispheres, P1- and P2-average curves were compared with the contralateral ones. These analyses were performed using a *t* test for dependent samples. Before performing a *t* test, both Levene's test and Brown-Forsythe's test were used to verify the equality of variances—a mandatory condition for *t* test analysis.

To calculate the latency interval between the exposure and significant changes in $[Hb tot]_{diff}$, a time series stepwise analysis was carried out for both sides. For each sampling point (every 1 s) after the onset of odor exposure, the mean values obtained from the 20 babies were compared to determine the cutoff point at which the average curves became significantly different from the baseline.

To evaluate interhemispheric differences in the change in Hb concentration, a comparison of $[Hb]_{diff}$ on the left and right sides was made. This was performed by a *t* test for independent variables.

Correlation matrices were used to measure the relationship between $[Hb]_{diff}$ and GA, PN, and PC.

Statistics were completed using the program Statistica (version 1998, StatSoft, Tulsa, OK, U.S.A.). A *p* value < .05 was considered statistically significant.

RESULTS

Panel Judgment of Intensity and Hedonic Value

The panel judged the intensity of the disinfectant to be significantly stronger than the smell of water and colostrum (ANOVA and Newman-Keuls posthoc comparison, $p < 0.001$ for both), but similar in strength to that of vanilla. The panel also rated water and colostrum as neutral ($p < 0.01$ versus Neomidil and Remove), and Neomidil and Remove as unpleasant and vanilla as pleasant (ANOVA and Newman-Keuls posthoc comparison, $p < 0.001$) (Fig. 3).

Newborns: Circulatory/Respiratory Responses to Olfactory Exposure

HR, RR, and peripheral SaO_2 did not change significantly during the P1 and P2 for either smell stimuli tested. No differences were noted between males and females.

Newborns: NIRS Data in Response to Olfactory Exposure

$[Hb O_2]$ and $[Hb tot]$ changed almost in parallel during NIRS registrations as a result of the small changes in $[Hb H]$. Thus, we have primarily limited our report to $[Hb O_2]$ changes.

Figure 3. Adult panel judgment of the two tested substances and comparison with three control substances. *Upper panel:* Intensity score. Vanilla, Neomidil, and Remove were scored as significantly more intense than colostrum and water ($p < 0.001$ for all comparisons). *Lower panel:* Pleasantness value. Zero indicates neutral. Neomidil and Remove were scored as unpleasant by the panelists compared with vanilla ($p < 0.001$), colostrum ($p < 0.01$), and water ($p < 0.01$). Columns represent mean values and whiskers standard errors. Statistical analysis has been performed by using ANOVA and Newman-Keuls posthoc comparison.

Neomidil odor (15 cases). Before the exposure (P1), only minor fluctuations around the baseline of $[Hb O_2]$, $[Hb H]$, and $[Hb tot]$ were observed. There were no differences between left and right sides. After the exposure, 13 of 15 babies responded with a significant decrease in $[Hb O_2]$ and $[Hb tot]$ in both sides ($p < 0.0001$). The changes of $[Hb H]$ were different: on the right side there was a nonsignificant increase compared with the baseline, whereas on the left side there was a significant decrease ($p < 0.05$). An example is shown in Figure 4. The difference between left and right response was highly significant ($[Hb H]_{diff}$ left versus right, $p < 0.0001$). A comparison between left and right sides showed a significantly larger decrease on the right side for both $[Hb O_2]_{diff}$ and $[Hb tot]_{diff}$ ($p < 0.01$ for $[Hb O_2]_{diff}$ and $p < 0.05$ for $[Hb tot]_{diff}$, respectively) (Figs. 5). Additionally, older babies tended to exhibit a diminished $[Hb tot]_{diff}$ in the right side (r value = 0.44, with 95% confidence interval).

The average curves for changes during exposure showed that the decrease in $[Hb O_2]_{diff}$ from the baseline started around 4 s after onset of exposure ($p < 0.05$) in the right side and around 6 s in the left side ($p < 0.05$) (Fig. 5).

Figure 4. Explicative case. Changes of $[Hb O_2]$ (top panel), $[Hb H]$ (middle panel), and $[Hb tot]$ (bottom panel) in one case after a 10-s exposure (dotted lines) to Neomidil. The decrease was more pronounced on the right side (solid circles) than on the left side (open squares). An analogous trace was seen after exposure to Remove. $[Hb tot]$ changes paralleled those of $[Hb O_2]$.

Remove odor (5 cases). The baseline did not show any major changes in any of the NIRS variables, and left and right recordings were not significantly different. After exposure to Remove, four out of five babies responded with a decrease in $[Hb O_2]$ and $[Hb tot]$, especially in the right hemisphere ($p < 0.01$) (Fig. 5). $[Hb H]$ decreased slightly on the left side (not statistically significant), whereas an increase was recorded on the right side. When comparing the $[Hb H]$ differences between pre- and postexposure, there was a significantly higher value of

Figure 5. Changes of $[Hb O_2]_{diff}$ after the exposure to the two tested substances Neomidil (top panel) and Remove (bottom panel). A 30-s period (corresponding to the differences, $P2 - P1$) has been analyzed. Although in some cases it was possible to follow the NIRS trace until the signal resettled itself around the baseline (as, for example, shown in Fig. 3), in most cases, this was impossible because of movement artifacts. The curves represent averaged line plots for $[Hb O_2]_{diff}$ changes both on the right (full squares) and the left (open circles) side.

$[Hb H]_{diff}$ on the right side ($p < 0.00001$). GA, PN, and PC were unrelated to the magnitude of $[Hb O_2]$, $[Hb H]$, and $[Hb tot]$ changes.

Similar to the Neomidil findings, $[Hb O_2]_{diff}$ started to decrease around 4 s after onset of exposure to Remove in both the right and left sides ($p < 0.05$ for both).

DISCUSSION

Newborn infants, especially in the NICU, are exposed to a range of artificial, unnatural olfactory stimuli. We have little, if any, idea of how such stimuli influence their brain function, activating neuronal circuits. Therefore, in our study, premature babies in controlled conditions were exposed to the smell of two commercially available solutions commonly used in the NICU (*i.e.* a disinfectant and an adhesive remover). The smell of both solutions was judged by an adult panel to be both strong and unpleasant.

The main finding of this study was that the odors of these two solutions elicited a decrease in blood oxygenation in an area likely to include the orbitofrontal olfactory area. This

change was different from that caused by exposure to colostrum and vanilla, which elicited an increase in blood oxygenation in the same region (9).

It has been assumed that neuronal firing *per se* (rather than cerebral metabolism alone) not only consumes oxygen, but also regulates r-CBF (28). Most functional studies using NIRS have therefore been based on the assumption that cortical activation is coupled with an increase in local cerebral blood volume, which is registered as an increase in [Hb O₂] and [Hb tot]. However, the Hb changes recorded by NIRS, after a certain stimulus, have been differently described. It has been shown that physiologic aging can influence Hb oxygenation in response to brain activation, as the increase in [Hb O₂] and [Hb tot] is less pronounced in elderly men (29). Moreover, Hoshi (30) described a decrease in [Hb O₂] in response to mental tasks. In addition, cortical activity was seen to be associated with a decrease in [Hb O₂] and [Hb H] levels in particular pathologic conditions, such as Alzheimer's disease (31). To reconcile these conflicting findings, it has been suggested that an increase in [Hb O₂] and [Hb tot] is seen when r-CBF exceeds oxygen consumption, whereas a decrease in [Hb O₂] and [Hb tot] occurs when the increased oxygen demand is not counterbalanced by an increased CBF in the illuminated area (14).

When interpreting the present data, it is also important to consider that unpleasant odorants can lead to cortical deactivation (32). Fransson *et al.* (33) recently investigated the correlation between deactivation and cerebral hemodynamics by magnetic resonance imaging, and they concluded that a state of cortical deactivation is associated with a decreased magnetic resonance signal, indicating a decrease in blood supply. Using the NIRS technique, a decrease in [Hb tot] has been defined as deactivation (13, 15, 34). If our data are analyzed according to this definition, the recorded decrease in [Hb O₂] and [Hb tot] might indicate a cortical deactivation related to the likely unpleasant olfactory stimulation. This finding would be supported by the [Hb H] increase on the right side, but not on the left where a [Hb H] decrease was observed. On neither side did the [Hb H] changes affect [Hb tot] concentration significantly.

In a recent study, Soussignan *et al.* (35) analyzed the neonate's olfacto-facial expression during different olfactory stimulations and concluded that behavioral markers of disgust (nose-wrinkling, upper lip-raising) discriminated some odors judged by adults to be pleasant with those judged to be unpleasant (*e.g.* vanillin *versus* butyric acid). However, despite some early similarity in processing olfactory stimuli's affective significance, there is no definitive evidence that newborns can discriminate between the hedonic valence of odors within the same perceptual range as adults.

In general, pleasant odors elicit approach behavior whereas unpleasant odors induce avoidance behavior. In both our first work (9) and the present work, we observed the newborn's behavioral reactions during exposure to the smells—although our observations were neither systematic nor quantitative. The general facial response of the newborns when exposed to the smell of the remover or the disinfectant consisted of an initial flaring of the nostril followed by nose-wrinkling, brow-

lowering, upper eyelid-lowering, and tendency to avoid the source of the smell by small head movements.

Substances containing different odorous compounds may have multiple targets in the brain cortex, including olfactory areas, olfactory-related areas, and other unrelated regions. Some compounds present in the fluids we tested, such as acetone, camphor, alcohol, and ether, may activate the trigeminal subsystem that seems to be fully receptive at 22 wk of gestation. Trigeminal subsystem contribution to the modulation of cerebral hemodynamics can be both indirect and direct. Parasympathetic projections arising from the sphenopalatine ganglion, which itself is innervated by trigeminal fibers (36), distribute through the ethmoid nerve to the cerebral vessels (37, 38). A considerable number of sensory trigeminal projections directly innervate cerebral blood vessels as collaterals from the same fibers that innervate the nasal cavity (39–41). These fibers project to second-order neurons in the trigeminal nucleus caudalis and its caudal extension into C1 and C2 cervical spinal cord (42). A trigemino-vascular system activation may play a major role in the response we observed by causing a redistribution of cerebral blood flow to certain areas of the brain, such as in the brain stem and upper cervical spinal cord, or the superior sagittal sinus. This may determine a [Hb O₂] and [Hb tot] decrease in the region that we have illuminated. The controversial results that we observed in [Hb H] changes may be related to differences in blood supply to those regions activated and deactivated by the different compounds.

Repetitive exposures to the same odor may affect the olfactory processing mechanisms (43) in both adults and newborn (44, 45). Thus, the number of times that each subject was exposed to Neomidil, Remove, or other substances containing analogous compounds might be an interesting factor to consider in further studies. In fact, newborns in NICU may be exposed to the smell of these substances several times a day. Although a systematic videotaping and analysis of the newborn's behavioral reaction was not performed, a common facial response as described above was been observed in the whole population irrespective of whether or not the infant had been exposed to the substance before.

The penetration depth of near-infrared light is higher in newborns than in adults. There is reason to believe that in the subjects we have studied the illuminated region included the more superficial cortex as well as deeper areas such as the amygdaloid cortex. This part of the brain—especially on the right side—seems to be involved in the perception of unpleasant smells (46). Interestingly, in our study, the right side exhibited a stronger response than the left in processing likely unpleasant odors.

Our findings have shown that a cortical response is elicited by exposure to odors that preterm infants often encounter in the NICU environment. They also have confirmed the ability of NIRS to explore functional activation of the brain cortex in the newborn. These hemodynamic changes are likely the result of a dynamic, physiologic regulation of r-CBF based upon the olfactory- and trigeminal-related areas of the brain. The dramatic functional response after exposure to common smells in an NICU underlines the sensibility and competence of the olfactory system in premature babies. The biologic significance

of exposure to unpleasant odors is unknown, but with regard to the close connections between olfactory cortex and centers regulating emotional state, it might be worth considering. This raises the question as to whether or not and to what degree certain smelling substances should be used in the NICU. Further investigations are needed to understand whether exposure to artificial, unpleasant odors can affect brain development and capacity to process smells.

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