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Review Article

Behavioral and Physiological Signs for Pain Assessment in Preterm and Term Neonates During a Nociception-Specific Response: A Systematic Review

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ABSTRACT

BACKGROUND/GOAL: Assessment and treatment of neonatal pain is difficult because current scales are rarely validated against brain-based evidence. We sought to systematically evaluate published evidence to extract validation of the most promising markers of neonatal pain.
METHODS: We searched four databases using germane MeSH terms. We focused on assessments of pain and/or nociception that had at least two measures among behavioral, physiological, or cortical components in preterm and/or term neonates. We evaluated studies for quality of evidence and strength of recommendations using standardized tools.
RESULTS: Fifteen articles met our inclusion criteria. Among the behavioral components uncovered in this review, the withdrawal reflex and changes in facial expression are the most strongly associated with nociception-specific brain activity. These associations may be influenced by gestational age and change over time. Physiological signs, such heart rate and oxygen saturation, have little to no association with this type of response.
CONCLUSIONS: Current assessments of neonatal pain include behavioral components that are associated with nociceptive processing, but also other less valid components, while omitting newer measures based on neuroscientific research.

Introduction

The neonatal period is a time of active brain development when early disruptions can have severe long-term consequences. Noxious somatosensory stimuli can alter processing of other senses that are critical to development[1] and persistent pain may have long-term effects on behavioral outcomes.[2] Evaluation and mitigation of pain is of particular concern in the neonatal intensive care unit, as infants can experience multiple daily skin-breaking procedures.[3,4] However, appropriate pain assessment in this preverbal population remains a challenge,[5] leading to a reliance on behavioral and/or physiological signs.

The first reliable infant behavioral pain measure was developed 30 years ago[6] and was later incorporated into several multidimensional scales. A recent integrative review revealed 29 pain assessment scales in preterm and full-term infants.[7] Many scales, such as the

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Premature Infant Pain Profile (PIPP),[8–11] integrate facial and physiological components in addition to nonpain related measures like gestational age. The parameters of this pain scale, along with those of the Neonatal-Infant Pain Scale (NIPS)[12] and the Modified Behavioral Pain Scale (MBPS)[13] are detailed in Table 1. A higher score for each respective scale is interpreted as a higher pain intensity. Despite a plethora of pain scales, many have incomplete psychometric testing, conflicting evidence with regards to their accuracy, and little evidence for their use in pain management.[14]

As no gold standard exists for the assessment of pain in infants, validation using brain-oriented methods has been investigated[15]; near-infrared spectroscopy (NIRS)[16] can measure superficial cerebral hemodynamic changes[17,18] while electroencephalography (EEG) and functional magnetic resonance imaging have provided direct evidence of pain-induced brain activity.[18–23] The former measures regional changes in oxygenated and deoxygenated hemoglobin concentration as a means to assess functional activation of the brain; a change in regional blood flow indirectly reflects underlying neural activity and provides a quantitative measure of cortical pain processing in the somatosensory cortex.[24–27] EEG is a direct measure of brain activity, with summed electrical impulse vectors that can generate localized amplitude changes specific to noxious stimuli in neonates.[19,23,28] The clinical practicality of these objective methods may be limited, but they provide a means to validate subjective or more feasible bedside neonatal pain assessment tools.

To date, no comprehensive study has utilized systematic review principles to evaluate neonatal pain assessment tools that incorporate behavioral and/or physiological components, in reference to brain-based methodologies such as NIRS, EEG, or functional magnetic resonance imaging. The current study aims to fill this gap in knowledge by determining the relative strengths of associations of pain scales and their components with pain-related brain activity.

Methods

Search strategy

Inclusion criteria: We included articles that contained an assessment of pain and/or nociception, and that had at least two measures within the following categories: behavioral, physiological, or cortical activity. The search focused on human subjects, either preterm or term births, but still within the neonatal period. Assessment and intervention studies were included. We further refined the definition of painful stimuli as skin-breaking procedures, to facilitate comparison and standardization. While other types of procedures may be considered painful, activation of C-fibers from direct mechanical trauma has been established as eliciting nociceptive rather than other types of somatosensory activity in humans and animals.[29–31]

Exclusion criteria: We excluded articles that consisted only of an abstract or poster without any published manuscript, as well as letters, editorials, lectures, books, or notes. We also removed studies containing subjects in the immediate perioperative period or requiring sedation on a ventilator. While the perioperative period usually includes nociceptive stimuli, it also includes the use of opioids as a mainstay for treatment, altering pain responses, and confounding assessments. Ethical considerations also make the study of such patients more difficult given that they may not warrant skin-breaking blood sampling when vascular access is already in place. Therefore valid comparisons were performed in patients who were not subject to exposure to systemic opioids, either directly or maternally sourced, and who underwent a clinically required skin-breaking procedure.

This systematic review was registered on PROSPERO (CRD42018099293). Details of the comprehensive literature review and databases are included in the supplementary materials. Supplementary Figure 1 shows the PRISMA flow diagram[32] outlining this process. Details of the respective search terms and final counts for each search are provided in Supplementary Table 1.

Data review, quality control, and grading recommendations

The reviewers then assessed independently the full text articles using an established QUADAS-2 tool[33] to rate the studies with regards to their bias and applicability, resolving any disagreements as needed. The outcome of this assessment is shown in Supplementary Table 2 and Supplementary Figure 2. We applied an adaptation of the Grading of Recommendations Assessment, Development, and Evaluation guidelines to inform the strength of recommendations compiled from the articles in this review.[34]

Results

Our systematic search and screening process yielded a final count of 15 studies, which included equal representation of NIRS[16,17,24,35–39] and EEG[40–46] monitoring. As these two reference modalities have differing resolution, depth, and types of cortical and/or subcortical activity detection, as well as widely different temporal resolution, we distinguished them for our initial evaluation of scientific quality and grading. These results are summarized (in reverse chronological order) in Tables 2 and 3. The NIRS-based category contained studies with a higher degree of heterogeneity among their protocols (see Fig 1) compared to the EEG-based category in which the bulk of the studies were derived from a relatively small group of investigators (see Fig 2). We included a more detailed description of the search results in the supplementary materials. These results did not lend themselves to a meaningful quantitative meta-analysis as they were too few and too heterogeneous, but did uncover data for qualitative associations.

In our systematic approach to develop recommendations regarding what behavioral and/or physiological parameters in current clinical practices of neonatal pain assessment may best approximate nociception-specific brain activity, we uncovered five individual parameters and three pain scales that are summarized in Fig 3. While the two reference standards in this review have intrinsic differences in their respective sensitivity and resolution, we provide an aggregate overview by considering factors such as the number of studies, sample sizes, quality of evidence, the strength of associations within the studies, and the level of agreement between them.

Withdrawal reflex

In terms of predicting nociception-specific brain activity, the withdrawal reflex is the most strongly associated and has the highest quality data among pain markers. Three EEG-based studies incorporated a measure of electromyography to this end.[41,44,46] The first study was limited to showing a significant increase in electromyography activity in response to

TABLE 1.
Pain Scales

	Component	pain Scales		
		PIPP	NIPS	MBPS
BEHAVIORAL	**Facial expression***	0-9 points	0-1 point	0-3 points
	Smiling			0
	Neutral or relaxed		0	1
	Grimace		1	2
	Brow bulge	0 [none]		
		1 [minimal]		
		2 [moderate]		
		3 [maximal]		3 [presence of
	Eye squeeze	0 [none]		brow bulge, eye
		1 [minimal]		squeeze, nasolabial
		2 [moderate]		furrow, plus open
		3 [maximal]		lips with or without
	Nasolabial furrow	0 [none]		reddened face]
		1 [minimal]		
		2 [moderate]		
		3 [maximal]		
	Cry	not included	0-2 points	0-4 points
	Laughing or giggling			0
	Not crying		0	1
	Moaning, quiet vocalizing or whimpering		1	2
	Vigorous cry or sobbing		2	3
	Full lunged cry, more than baseline cry†			4
	Movement	not included	0-2 points	0-3 points
	Usual movements or resting/relaxed		0 [arms and legs]	0
	Flexed/extended		1 [arm(s) or leg(s)]	
			2 [arm(s) and leg(s)]	
	Attempt to withdraw limb			2
	Complex agitation involving head, other limbs or rigidity			3
	State of arousal or behavioral state	0-3 points	0-1 point	not included
	active/awake, eyes open, facial movements	0	0 [sleep/awake]	
	quiet/awake, eyes open, no facial movements	1	1 [fussy]	
	active/sleep, eyes closed, facial movements	2		
	quiet/sleep, eyes closed, no facial movements	3		
PHYSIOLOGIC	**Breathing**	not included	0-1 point	not included
			0 [relaxed]	
			1 [changed pattern]	
	Heart rate increase (beats per minute)	0-3 points	not included	not included
		0 [0-4]		
		1 [5-14]		
		2 [15-24]		
		3 [≥ 25]		
	Oxygen saturation decrease	0-3 points	not included	not included
		0 [0%-2.4%]		
		1 [2.5%-4.9%]		
		2 [5%-7.4%]		
		3 [≥ 7.5%]		
OTHER	**Gestational age**	0-3 points	not included	not included
	≥ 36 weeks	0		
	32 to < 36 weeks	1		
	28 to < 32 weeks	2		
	< 28 weeks	3		
	TOTAL SCORE	**0-18 points**	**0-7 points**	**0-10 points**

Not all components are included in each scale, as denoted by black spaces in the respective pain scale columns. One number is assigned for each included component based on the presence of criteria in the left-hand column or condition listed in brackets, with exception of PIPP, which grades subcomponents for facial expression individually. The number for each component is summed to a total score such that higher scores are interpreted as higher pain intensity.

* For PIPP, the degree of brow bulge/eye squeeze/nasolabial are based on percentage of time that they are present: none (0%-9%), minimal (10%-39%), Moderate (40%-69%), Maximal (≥ 70%).
† Scored only if there is a cry at baseline.MBPS = modified behavioral pain scale; NIPS = neonatal infant pain scale; PIPP = premature infant pain profile.

a heel lance,[41] whereas more recent work showed significant correlation ($R^2 = 0.281$, $P = 0.001$) between nociceptive reflex withdrawal activity and nociception-specific brain activity.[44] Measurable reflex does not always translate into visible limb movement, which depends on stimulus intensity and was reported to occur in up to 72.5% of cases at a higher intensity. This level of stimulation was also able to elicit a significant reflex withdrawal in the contralateral limb. A study of preterm infants revealed that the withdrawal reflex became more refined with increasing gestational age.[46] This maturing

TABLE 2.
NIRS-Based Studies

Study ID	Infant Population	n	Stimuli	‡GA (Weeks)	‡Postnatal Age (Days)	Reference Measures and Locations	Index Tests	Association	†Quality
Olsson et al.[37]	PT neonates in NICU; healthy	10	Sham, Venipuncture	30.7 [26.6-33.9]	6.6 [±4.7, 1-18]	HbO_2, HHb; somatosensory cortices	**PIPP-R**	NS, changes in HbO_2 with no change in PIPP-R score	Moderate
Hwang et al.[35]	PT neonates in NICU; RDS, TTN or other	24	Heel lance	31.1 [±2]; 32.6 [±2.4	2.0 [±0.0]; 1.8 [±0.4]	$rScO_2$, cFTOE; middle of forehead	**PIPP** ***HR** ***SpO_2**	Positive; increased after stimulus NS change NS change	High
Beken et al.[39]	Term births in NICU; Jaundice	25	Venipuncture	Median: 38.0 [37.0-40.0]; 38.0 [37.1-40.5]	Unspecified	HbO_2, HHb, HbT, CBV, CBF, TOI; left frontoparietal	**NIPS**	Undetermined, no baseline scores were recorded	Very Low
Bembich et al.[36]	Term neonates in unspecified setting; Healthy	30	Heel lance	38-41	3	HbO_2; bilateral parietal, temporal and posterior frontal cortices	**NIPS**	NS, change in cortical activity may be present with no change in NIPS and vice versa	Low
Ozawa et al.[38]	PT and term neonates in nursery and NICU; Clinically stable	80	Venipuncture	39.3 [±1.2, 37-41]; 38.9 [±1.4, 37-41]; 34.0 [±2.5, 26-36]	5.0 [±0.3, 4-6]; 7.0 [±3.0, 5-15]; 25.7 [±24.0, 5-107]	HbO_2, HHb; forehead, over eyebrows bilaterally	**PIPP**	Depends on GA and pain exposure; positive at term for facial expression ($R^2 = 0.14$ to 0.28) and total score ($R^2 = 0.16$ to 0.24), but not for physiologic score; positive at PT only if previously exposed to pain, for physiologic score ($R^2 = 0.13$ to 0.17) and partially for total score (R^2 = NS to 0.16), but not for facial expression	High
Slater et al.[24]	PT neonates and infants in NICU; Clinically stable	12	Heel lance	24.0-34.6	5-134	HbT, HbO_2, HHb; bilateral somatosensory cortices	**PIPP** ***Facial expression** ***Physiologic score**	Positive ($R^2 = 0.320$); increased after stimulus; change in brain activity is more strongly linked to behavioral components ($R^2 = 0.554$) than to physiologic components ($R^2 = 0.158$) Changes may be absent even during a positive brain response Does not improve correlation when added to facial expression	Moderate
Bartocci et al.[17]	PT neonates in NICU; RDS, TTN, HG	40	Disinfection (tactile), Venipuncture	32.0 [±3.0, 28-36]	1.3 [±0.2, 1.04-1.75]	HbO_2, HHb, HbT; somatosensory cortices and occipital cortices	**HR** **SpO_2**	Positive, but only transient increase and otherwise NS change and unrelated Negative, but only transient decrease in SpO_2 while HbO_2 remains elevated	High
Bucher et al.[16]	PT births in neonatal intermediate care setting; unspecified diagnoses	16	Heel lance	27-34	Unspecified	HbO_2, HHb, HbT, CBV; temporal region	**HR, Breaths, Cry**	All index tests: no clear relationship to reference, which also showed variable results	Very Low

* Parameters that were also quantified and assessed independently of the pain scale.
† Graded as very high, high, moderate, low, or very low based on assessment of study conduct using the QUADAS-2 tool.[33]
‡ Expressed as mean with ± standard deviation and/or range, unless otherwise specified.CBF = cerebral blood flow; CBV = cerebral blood volume; cFTOE = cerebral fractional tissue oxygen extraction = [SpO_2-$rScO_2$] / SpO_2; GA = gestational age (postconceptual); HbO_2 = oxyhemoglobin; HbT = total hemoglobin; HHb = deoxyhemoglobin; HG = hypoglycemia; HR = heart rate; n = number of samples; NICU = neonatal intensive care unit; NIPS = neonatal infant pain scale; NS = nonsignificant; PIPP = premature infant pain profile; PIPP-R = PIPP-revised; PT = preterm; RDS = respiratory distress syndrome; $rScO_2$ = regional cerebral oxygen saturation; SD = standard deviation; SpO_2 = oxygen saturation; TOI = tissue oxygenation index; TTN = transient tachypnea of newborn.

TABLE 3.
EEG-Based Studies

Study ID	InfantPopulation	n	Stimuli	‡GA (weeks)	‡Postnatalage (days)	ReferenceMeasures and§Locations	Index Tests	Association	†Quality
Maitre et al.[42]	Term neonates in newborn nursery; Healthy	54	Air puff, cold, Heel lance	Median [IQR]: 39 [38-40]	1-3	ERP amplitude; Channels: F3,F4,C3, C4 G: Unspecified; Ref: Cz	**Cry**	NS difference in cortical responses based on presence or absence of audible cry; lack of association between cry amplitude characteristics and amplitudes of ERP responses	Very high
Hartley et al.[45]	PT and term neonates in maternity unit, special care unit and outpatient clinic; Clinically stable	28	Heel lance, Non-noxious control	36.1 [35.1-36.6]; 38.6 [36.4-40.9]	18 [2.8-25]; 4.5 [1.8-25.3]	PCA; Channels: FCz,T3,C3, Cz,C4, T4,CPz,Oz G: forehead; Ref: Fpz,Fz	**PIPP** **Grimace**	Stimulus did not evoke change in facial expression in 39% of cases, and of those, 45% showed significant increase in noxious-evoked brain activity. Positive, increased after stimulus, significant correlation ($R^2 = 0.152$, $P = 0.038$).	Very High
Hartley et al.[46]	PT and term neonates in maternity and neonatal units; Stable, history of IVH, PNI, NEC or surgery	40	Heel lance	Median [IQR]: 34.4 [29.6-40.6], 28-42	12.1 [±11.1]	PCA; Channels: FCz,T3,C3, Cz,C4, T4,CPz,Oz G: forehead; Ref: Fpz,Fz	**EMG**	Maturation of brain activity is related to refinement of the withdrawal reflex; ratio increases with GA ($P = 0.024$, $\beta = 0.054$), not postnatal age.	Very high
Hartley et al.[44]	Term neonates in maternity unit and special care baby unit; Clinically stable	12	Pinprick, Heel lance	37-42	< 10	PCA; Channels: FCz,T3,C3, Cz,C4, T4,CPz,Oz G: forehead; Ref: Fz	**PIPP** **EMG**	NS increase in pain score in the context of an evoked nociceptive-specific pattern of brain activity. Positive, increased after stimulus, significantly correlated ($R^2 = 0.281$, $P = 0.001$)	High
Verriotis et al.[43]	Term infants in outpatient clinic; Healthy	15	Needle puncture (innoculation)	38.9 [±1.7]; 40.0 [±1.2]	43 [±18]; 374 [±9]	ERP amplitude; Channels: Fp1,Fp2, F3,Fz,F4, T3,C3,Cz,C4, T4,CP3,CPz,CP4, T5, T6,POz,O1,O2 G: forehead; Ref: FCz	**MBPS**	No correlation; Spearman rank order correlation coefficients: $\rho = -0.15$ ($P = 0.62$) $\rho = -0.20$ ($P = 0.52$)	Very high
Slater et al.[41]	Term neonates in postnatal ward; Healthy	44	Heel lance, Non-noxious control	39.8 [±1.1]; 39.8 [±1.3]	3 [±2]; 2 [±2]	PCA; Channels: Fp1,Fp2, F7,F3,Fz, F4,F8,FT9, FC5,FC6,FT10,T7, C3, Cz,C4,T8,CP5,CP3, CPz, CP4,CP6,P9,P3, Pz,P4,P10, PP07,POz, PP08,O1,Oz,O2 G: chest; Ref: FCz	**PIPP** ***HR** ***SpO2** **EMG**	NS; nociceptive-specific brain activity may be detected in the absence of any change in facial expression NS change NS change Positive; increased after stimulus	Very high
Norman et al.[40]	Term neonates in maternity unit; Healthy	72	PinPrick, Heel lance, Venipuncture	40 [39-42]; 39.5 [37-41]; 40 [38-41; 40 [37-41]	2.8 [1.8-3.5]; 2.4 [1.5-3.9]; 5.0 [4.0-6.0]; 2.9 [2.5-3.4]	FFT, aEEG, asymmetry index, TF analysis; Channels: F3,F4,Cz, P3,P4 G: Unspecified Ref: Unspecified	**PIPP**	NS; while P values are low, F3-Cz ($R^2 = 0.163$, $P < 0.001$), F4-Cz ($R^2 = 0.171$, $P < 0.001$), F3-P3 ($R^2 = 0.293$, $P < 0.001$), F4-P4 ($R^2 = 0.238$, $P < 0.001$), response is reported to be more so from muscle activity rather than from the cerebral cortex.	Moderate

* Parameters that were also quantified and assessed independently of the pain scale.
† Graded as very high, high, moderate, low, or very low based on assessment of study conduct using the QUADAS-2 tool.[33]
‡ Expressed as mean with ± standard deviation and/or range, unless otherwise specified.
§ Channel location/nomenclature is based on the 10-20 system.aEEG = amplitude-integrated EEG; EMG = electromyography (spinal reflex); FFT = Fast Fourier transformation; G = ground electrode location; GA = gestational age (postconceptual); HR = heart rate; IQR = inter-quartile range; IVH = intraventricular hemorrhage; MBPS = modified behavioral pain scale; n = number of samples; NEC = necrotizing enterocolitis; NS = nonsignificant; PCA = principal component analysis; PIPP = premature infant pain profile; PNI = postnatal infection; PT = preterm; ; Ref = reference electrode location; SD = standard deviation; SpO_2 = oxygen saturation.

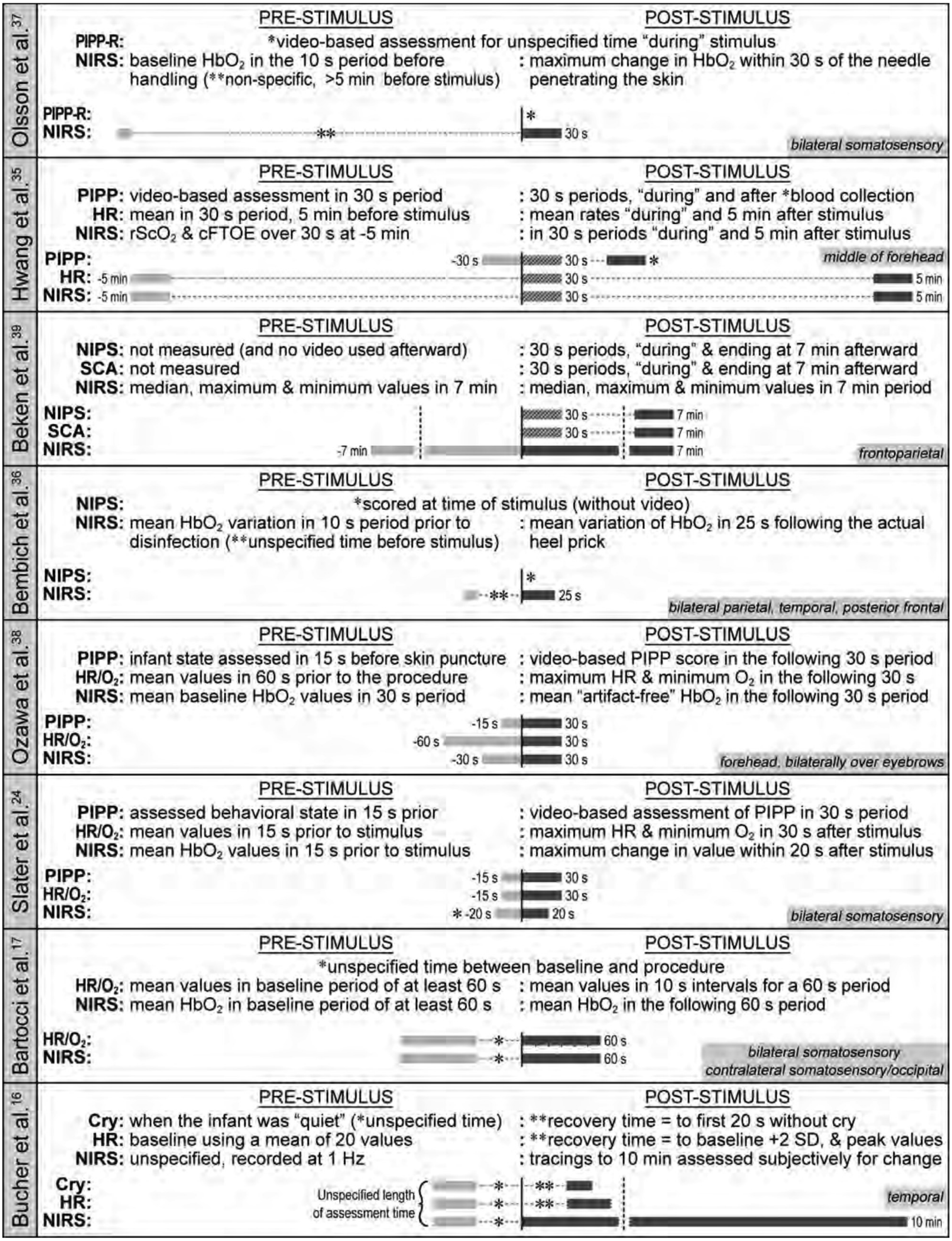

FIGURE 1.
Schematics for NIRS-based protocols, showing before (light gray), during (striped) and after (dark gray) the stimulus. Location of sensor is denoted in the lower right gray box for each respective study. SCA = skin conductance algesimeter.

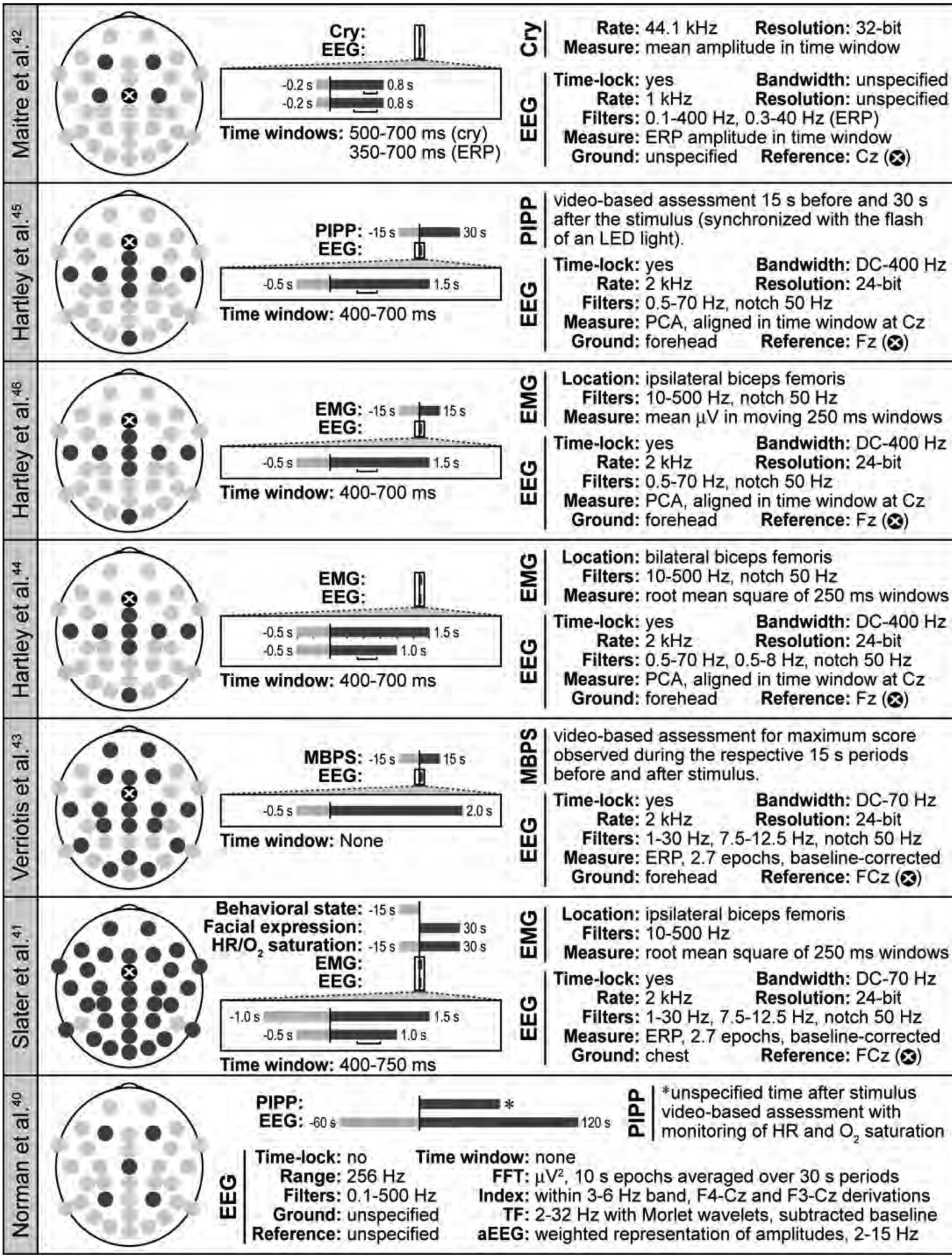

FIGURE 2.
Schematics for EEG-based protocols, showing before (light gray) and after (dark gray) the stimulus. Location of electrodes are denoted in the left (nasion on top) for each respective study. TF = time frequency analysis.

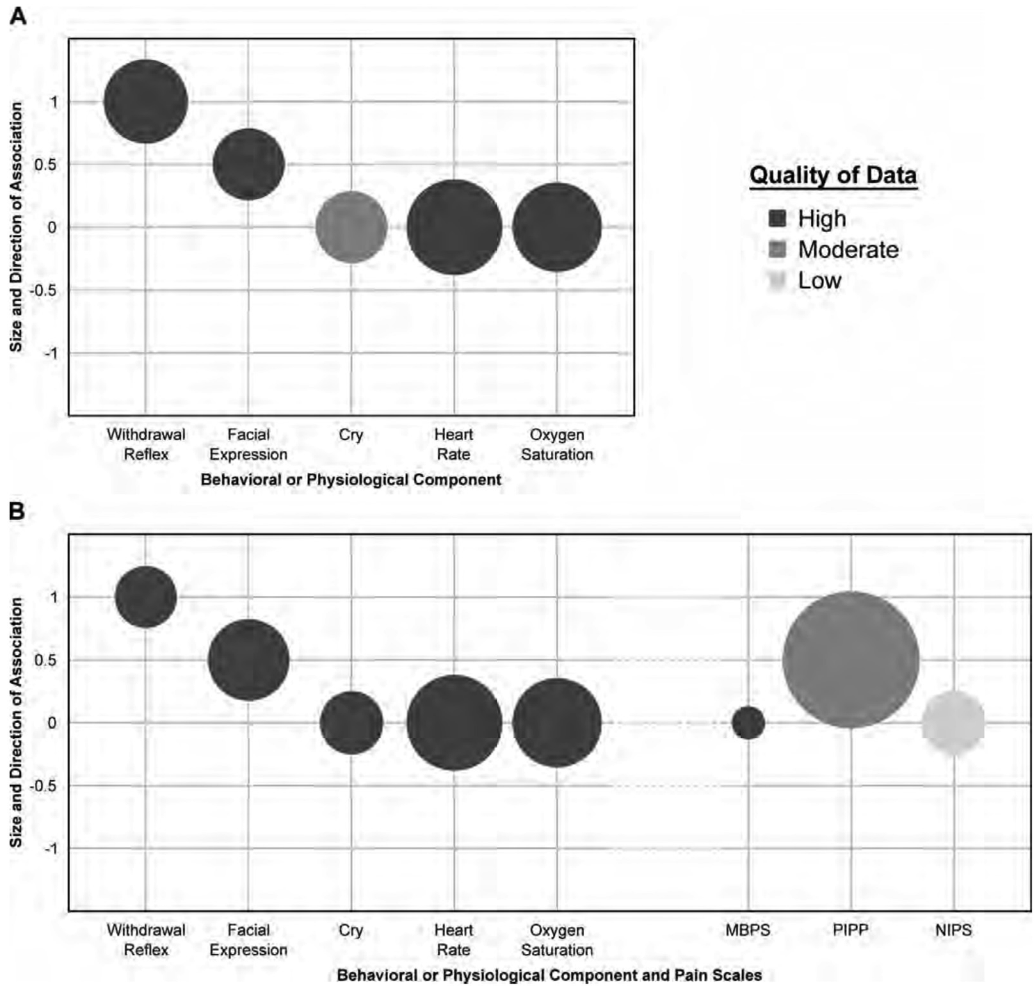

FIGURE 3.
Relative association of behavioral and physiological components and pain scales to cortical activity. Each measure listed on the horizontal axis is compared to pain-related brain activity. The relative positivity and negativity along the vertical axis represents the degree of a positive and negative association, respectively. The size and color of each circle represents the relative quantity and quality, respectively, of data that contribute to each given association. (A) Association to the presence or absence of a pain-related cortical response; (B) association to the intensity of a pain-related cortical response.

response coincided with an increased magnitude of nociception-specific brain activity, resulting in a significant increase of its relative proportion to reflex withdrawal activity at the individual level ($\beta = 0.054$, $P = 0.024$). Reported changes in brain activity could not be accounted for by postnatal age or estimated cumulative prior pain exposure.

Facial expression

There was a weak association due to a higher degree of consensus among results in term infant studies. The quality of data was relatively high, but consisted of only two studies, one NIRS-based and the other EEG-based.[38,45] The former reported no significant relationship between changes in facial expression and brain activity in preterm infants,[38] whereas the latter pooled the preterm population together with term infants to derive a significant positive correlation ($R^2 = 0.152$, $P = 0.038$).[45] Similarly, the NIRS-based study reported a positive correlation among term infants who underwent venipuncture (left: $R^2 = 0.137$, $P = 0.044$; right: $R^2 = 0.281$, $P = 0.003$), but only for those who did not have a previous painful experience.

Comparable to the withdrawal reflex, changes in facial expression, or lack thereof, were not completely reliable in determining the presence or absence of a nociception-specific response in the brain. Even in video-based protocols in which judgment of changes in facial expression was somewhat objectified, over one-third of cases had no changes in facial expression in the context of a nociception-specific response. The reverse also held true, in that about one-quarter of infants with changes in facial expression did not have any related detectable changes in brain activity.[45]

Cry, heart rate, oxygen saturation

There was consistent agreement among the studies regarding lack of association between cry, heart rate, and oxygen saturation as they relate to nociception-specific brain activity. This general consensus spanned NIRS-based and EEG-based work, and in preterm and term populations. A single NIRS-based investigation of cry in preterm infants measured recovery time of crying after a heel lance, making recommendations for this particular use of cry challenging at this time. The aggregate data were consistent with the recommendation that adding a physiological score to facial expression score did not improve the correlation of the PIPP score to the cortical response.[24]

Pain scales

Among the three pain scales included in this review, the PIPP was the most widely studied. However, an obvious dichotomy exists between NIRS-based and EEG-based results for this scale. While this may be attributable to the contrasting technologies, such a disagreement between reference standards was only apparent for the PIPP as a whole and not for its individual components. Notably, the bulk of the studies that examined PIPP were NIRS-based, with heterogeneity in experimental protocols when compared to their EEG-based counterparts. EEG-based studies of the PIPP included term infants only. None found significant correlations between the PIPP score and brain activity, except for the one that was not time-locked and that attributed the positive signal to be a contaminant from muscle activity.[40] Despite these concerns, multiple studies from independent investigators reported some correlation.

Two NIRS-based studies reported coefficients of correlation. Ozawa et al. reported correlations that depended on gestational age and/or previous exposure to painful procedures.[38] Their findings included positive correlations between brain activity and the total PIPP score (left: $R^2 = 0.160$, $P = 0.03$; right: $R^2 = 0.240$, $P = 0.006$) in term infants, but only partially in preterm infants (left: $R^2 = 0.160$, $P = 0.03$; right: R^2 = nonsignificant) and only if the latter had a previous exposure to a painful stimulus. Slater et al. combined both preterm and term infants to report a positive correlation between PIPP score ($R^2 = 0.320$) and brain activity,[24] with changes in the latter being more strongly linked to behavioral components ($R^2 = 0.554$) than to physiological components ($R^2 = 0.158$). A third study that included only preterm infants also supported a positive association.[35] Correlations between PIPP scores and prematurity are especially problematic, notably when the proportion of the variance in scores is low; the PIPP incorporates gestational age into score calculation, confounding associations. Mechanistic studies of the underpinnings of cortical pain processing in preterm infants do not support a linear relationship with gestational at birth or even postnatal age.[19]

The most recent NIRS-based study applied a revised version of PIPP (PIPP-R)[9] that showed no significant correlation to NIRS monitoring over bilateral somatosensory cortices.[37] PIPP-R minor revisions included changes to the physical layout, detailed instructions for use, and clarification of scoring gestational age and behavioral state indicators for preterm and term infants. While most patients that contributed PIPP data were preterm infants, positive correlations were also derived among term infants, in agreement with previous validation of this pain assessment tool in the latter population.[11] In contrast, the two studies of the NIPS, which consist almost exclusively of behavioral components, failed to establish a similar correlation.[36,39] However, these latter two studies were of relatively low quality for the purposes of this review. An assessment of the MBPS as it compares to the cortical EEG response during an inoculation procedure also failed to show any relationship.[43]

Discussion

This is the first systematic review of the aggregate data pertaining to behavioral and physiological components of neonatal pain assessment as they relate to measures of nociception-specific brain activity. The logistics surrounding the timing and interpretation of NIRS-based and EEG-based technologies limit their clinical feasibility, which to date restricts their use mainly to fields of research. Appropriate application of either of these modalities requires advanced training, sensitive equipment, computing technology, and measurements that need to be precisely time-locked to related stimuli. However, they have great potential to expand the current knowledge base by providing an objective means to studying nociception, pain assessment, efficacy of its treatment, as well as for validation of the more subjective tools that are used in this regard.

While HR and SpO_2 are commonplace in many of the pain scales that are applied in the clinical setting,[9,47–52] none of the studies that have a coinciding brain-oriented measure support a correlation with the latter. The lack of association between the presence and/or amplitude of cry with pain-related brain activity presents a concern regarding those pain scales that incorporate this parameter.[13,47,48,53–59] While the withdrawal reflex has the most promise to date in terms of its association with brain-oriented measures of nociception, important contextual considerations include gestational age and intensity of stimulus. Another caveat is that these data were all derived from the same group of investigators, but their high-quality systematic approach provides strength to the recommendation in that they were able to generate a statistically significant coefficient of determination.[44] Inconsistencies among studies that examined changes in facial expression limited the strength of the recommendation for using this parameter to represent nociception-specific brain activity. However, with an appreciation that term infants who are facial nonresponders may still be experiencing nociception, changes in facial expression appears to be a relatively strong component of current pain assessment tools. This finding may not hold true in preterm infants. The contrasting data surrounding the PIPP as it relates to associated brain activity suggest that this tool needs to be further refined as there is significant disparity between NIRS-based and EEG-based studies.

Altogether, this review shows that no individual behavioral or physiological component is adequate in alerting to the presence of pain responses that occur on a cortical level. This supports the need for multidimensional assessment tools, but also raises the concern that neonatal pain may be mistreated if its assessment is based on tools that have incomplete psychometric testing or that do not consider developmentally important cues. For example, while half of PIPP scoring is based on assessments of facial expression, it does not factor in body movements or the reliable withdrawal reflex. Given that one-third of the PIPP score is derived from physiological components, it is also susceptible to being inaccurate for reflecting patients' pain. Similarly, the relative weight that NIPS and MBPS place on less reliable components, along with the unavoidable subjectivity that factors into their overall scoring, leaves these scales prone to error. Counterbalancing their questionable validity, these scales are clinically practical with achievable intra- and inter-rater reliability. Therefore next steps in this field should focus on integrating objective measures, as feasibility permits, that will serve to supplement or replace current clinical practices. The design of a template in recent EEG-based studies offers the opportunity for validating neonatal pain assessment tools and assisting in future development of objective brain-oriented measures of neonatal pain.

Limitations of the review

There were relatively few studies that combined brain-based measures and behavioral and/or physiological components, but they were mostly of high quality. For EEG-based data, many were obtained in related research groups, potentially introducing bias; however, these groups also maintained high scientific rigor in their protocols. In contrast, NIRS-based protocols were relatively heterogeneous, making aggregate data between the two methodologies more difficult. While both may be able to quantify and distinguish innocuous vs noxious evoked activity at a group level, novel single-trial analysis has shown that hemodynamic and electrophysiological responses do not always co-occur at an individual level.[60] This at the very least indicates the need for integrated and multimodal brain monitoring.

Conclusions

This systematic review uncovered a total of 15 studies that included behavioral and/or physiological components along with some measure of nociception-related brain activity. While NIRS- and EEG-based studies were equally represented, they were not similar in methodologic rigor. Nevertheless, some trends could be derived from areas of agreement between these two categories, which did not favor the use of physiological components (HR and SpO_2) to measure pain. The withdrawal reflex and targeted changes in facial expression provided observable measures that may be associated with a nociception-specific response, but cry presence and amplitude were not. While the PIPP is one of the most established instruments for assessment of neonatal pain, the conflicting evidence in this review suggest some of its components may be of little relevance when measuring nociceptive processing. Further studies should focus on validation of scales with the components most likely to represent evidence of pain and assess the ability of the scales to respond to pain mitigation.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.pediatrneurol.2018.10.001.

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