Pain assessment during eye examination for retinopathy of prematurity screening: Skin conductance versus PIPP-R

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Abstract

Aim. To assess changes in skin conductance during retinopathy of prematurity screening and to study the correlation between the skin conductance and a validated pain scale.

Methods. Prospective observational study. Fifty-three eye examinations were performed in 32 preterm infant candidates for retinopathy of prematurity screening. Outcome measures were changes in Premature Infant Pain Profile-Revised (PIPP-R) scale and number of skin conductance fluctuations.

Results. There was a significant increase from baseline in the number of skin conductance fluctuations and PIPP-R during the procedure. The maximum value of number of skin conductance fluctuations was 0.64 ± 0.44 peaks/sec, and the maximum value of PIPP-R was 10.8 ± 3.3.

A correlation between the skin conductance and PIPP-R was not found at any time during the eye examination. Repeated measures correlation analyses showed only a moderate positive correlation between PIPP-R and number of skin conductance fluctuation values.

Conclusión. There were significant changes in both PIPP-R and number of skin conductance fluctuations during retinopathy of prematurity screening, reaffirming that this procedure is painful and stressful. The number of skin conductance fluctuations and PIPP-R are not significantly correlated, which likely reflects that these parameters evaluate different but complementary aspects of neonatal pain responses.

Keywords: pain, premature infants, retinopathy of prematurity, skin conductance, stress

Abbreviations

ROP, Retinopathy of prematurity; AAP, American Academy of Paediatrics; SC, Skin conductance; PIPP-R, Premature Infant Pain Profile Revised; GA, Gestational age; NSCF, Number of skin conductance fluctuations

Key Notes

- Pain assessment is still a challenge in the neonatal population.
- During retinopathy of prematurity (ROP) screening, there is a significant increase in the number of skin conductance fluctuations (NSCF) and PIPP-R scores from baseline.
- There is no consistent correlation between NSCF and PIPP-R, which probably reflects that they evaluate different but complementary aspects of neonatal pain responses.

1 INTRODUCTION

Neonates, including preterm infants, are sensitive to nociceptive stimuli and pain during the neonatal period has both short- and long-term adverse consequences.[1,2] Nevertheless, newborns admitted to neonatal units are still exposed to hundreds of painful procedures during their hospital stay.[3] One of these procedures is the retinopathy of prematurity (ROP) screening. ROP is a serious complication of preterm birth that potentially leads to visual disability or blindness. Therefore, screening programmes aimed at detecting ROP in early stages are widely recommended, and at-risk infants should receive eye examinations on a scheduled basis.

Eye examinations can cause distress and pain, as far as they are associated with a number of behavioural and physiological effects: changes in facial expression and heart rate, apnoea, feed intolerance, increased oxygen requirements, etc In fact, the recent 2018 American Academy of Paediatrics (AAP) statement on ROP screening recommends that efforts should be made to minimise the discomfort and systemic effect of the examination,[4] and it is imperative to investigate novel approaches to reduce pain in this setting.[5] However, there is still no gold standard for the evaluation and treatment of pain during ROP screening.[5,6]

One limitation to achieving adequate pain management in newborns is the fact that pain assessment is difficult in this population. Although multiple pain scoring systems exist, there is no universal approach to assessing neonatal pain, and even with the widely recommended use of clinical scales, accurate pain assessment remains a challenge in neonatology, and there is still a need for more objective and reliable tools.

Skin conductance (SC) is one of the multiple emerging technologies used to measure pain responses. SC is based on the principle of emotional sweating, and the changes in SC reflect changes in the sympathetic activation of sweat glands. Previous studies have shown that SC can detect reactions to procedural pain in newborns,[7-9] children [10,11] and adults,[12] but whether SC can serve as a diagnostic tool for neonatal pain at the bedside should still be elucidated.

Hence, the purpose of this study was to assess changes in SC during ROP screening and to study the correlation between the SC and a validated pain scale, the Premature Infant Pain Profile-Revised (PIPP-R). Our hypothesis was that changes in SC will correlate with changes in PIPP-R.

2 METHODS

This study was a prospective observational study conducted from June to December 2017 in a level III neonatal unit.

2.1 Participants and procedure

Infants with a birthweights ≤1500 g or gestational age (GA) ≤32 weeks were candidates for retinal screening according to national recommendations. All examinations were performed after pupillary dilation by the same paediatric ophthalmologist using binocular indirect ophthalmoscopy and a 24-dioptre lens. The ophthalmologist was assisted by two nurses: the neonatal nurse responsible for the patient care that particular day and one specific pain study

nurse. A lid speculum was placed in all cases, and scleral depression was performed as needed. For pupillary dilation, topic 0.5% cyclopentolate and 2.5% phenylephrine were used 30-60 minutes before the procedure.

According to the local protocol, both pharmacological and non-pharmacological pain relief measures were applied: swaddling, facilitated tucking, a quiet environment, non-nutritive sucking, oral paracetamol (15 mg/kg, 30 minutes before the procedure), 24% oral sucrose, topical anaesthetic eye drops (tetracaine and oxybuprocaine) and lubrication with normal saline.

2.2 Skin conductance

Skin conductance was analysed by a Med-Storm monitor® (Med-storm Innovation, Oslo, Norway) and a 3-electrode system applied to the sole of the foot according to manufacturer's specifications. We choose as main outcome measure of SC the number of SC fluctuations (NSCF) per second, which has been found to be the most sensitive parameter of SC to detect stress and pain in newborns. A more extensive description of the SC monitor and NSCF has been previously reported.[7] The NSCF in peaks/sec was recorded at four predefined time points during examination of the first eye: at baseline, at blepharostat insertion, at scleral indentation and at the end of the procedure. Measurements of NSCF were analysed at thirty-second intervals during which the maximum peaks/sec were registered. This interval was chosen because it was previously used in preterm infants to assess SC pain responses[13] and because in a previous pilot study, we observed that SC changes last approximately 30 seconds after the beginning of the predefined time period.

2.3 Physiological variables

All patients were monitored continuously using a Masimo Radical 7® (Masimo, Irvine, California, USA) pulse oximeter. Episodes of tachycardia (>180 bpm), bradycardia (<100 bpm) and oxygen desaturation (<85% for >10 seconds) were registered.

2.4 PIPP-R

The PIPP score is a multidimensional 7-indicator pain assessment tool that includes behavioural, physiological and contextual indicators. This score is determined by assigning 0 to 3 points to each indicator. Final scores range from 0 to 21, with higher scores indicating more intense pain responses. This scoring system was widely validated.[14,15] PIPP-R is a revised modification of PIPP aimed at enhancing validity and feasibility, which makes it easier to use in clinical practice.[16,17] The main variation of PIPP-R with respect to PIPP is that GA and basal behavioural state are scored after the procedure only if there are changes in any of the other indicators.

Two investigators with special training with the PIPP-R tool recorded the scores of behavioural and physiological variables at the four prespecified time points during examination of the first eye, reaching a consensus. Total PIPP-R scores were calculated after the procedure.

To further explore the different components of the PIPP-R, subtotal scores for physiological variables (scores range from 0 to 6) and for behavioural variables (scores range from 0 to 9) were recorded.

2.5 Sample size calculation

A sample size of 50 examinations allows us to achieve a power of 80%, with an alpha of 0.05, to detect as statistically significant a correlation coefficient of 0, 4 or higher.

2.6 Statistical analysis

Continuous variables are expressed as the mean ± standard deviation, and categorical variables are presented as absolute number and percentage. The Wilcoxon signed-rank test was used to compare SC and PIPP-R between baseline and the three predefined time points. The Mann-Whitney test was used to determine whether there were significant differences in NSCF or PIPP-R between groups.

Pearson's r and Spearman's rho correlation tests were used to study both linear and non-linear correlations between PIPP-R and NSCF at each time point, as well as between their maximum values during the procedure. To assess the overall association between PIPP-R and NSCF across the four measurements, repeated measures correlation was calculated using the *rmcorr* package with R software.[18] Statistical analysis was performed with SPSS 24.0 and R (version 3.5.1) statistical software. A bilateral *P*-value of <.05 was considered statistically significant.

The study protocol was approved by the local research ethics committee, and informed parental consent was obtained before inclusion in the study.

3 RESULTS

The study sample included 53 eye examinations performed in 32 patients (14 girls and 18 boys) with a mean GA at birth of 30.2 ± 1.2 weeks and 35.5 ± 1.9 weeks at the time of examination. Table 1 contains a summary of demographic details of the infants in this study.

There was a significant increase in the NSCF and PIPP-R from baseline to both lid speculum insertion and scleral indentation (Figure 1). The mean of the maximum value of NSCF during the examination was 0.64 ± 0.44 peaks/sec, and the mean of the maximum value of PIPP-R was 10.8 ± 3.3. A total of 25 patients (47.2%) showed PIPP-R scores >12, and 39 patients (73.6%) showed NSCF >0.4 peaks/sec.

In 39 out of the 53 examinations (73, 6%), the infants experienced episodes of tachycardia; in six examinations (11.3%), the infants experienced episodes of bradycardia; and in 23 examinations (43.4%), the infants experienced episodes of desaturation.

There were no statistically significant differences in the maximum NSCF between the patients with and without tachycardia (0.62 ± 0.42 vs 0.69 ± 0.49 P = .6), with and without bradycardia (0.84 ± 0.62 vs 0.62 ± 0.41 P = .24) and with and without episodes of desaturation (0.72 ± 0.42 vs 0.58 ± 0.45 P = .23) or between the first and successive examinations (0.6 ± 0.46 vs 0.7 ± 0.4 P = .45).

A correlation between the SC and PIPP-R was not found at any time, with complete PIPP-R, or with the behavioural or physiological components of the scale (Table 2, Figure 2). This result indicates that patients with higher PIPP-R values do not necessarily present higher NSCF determinations. Examinations with maximum PIPP-R scores >12 showed similar maximum NSCF values (0.65 ± 0.4 vs 0.63 ± 0.48 peaks/sec, P-value .763).

Repeated measures correlation analyses showed a moderate positive correlation between PIPP-R and NSCF values (r_m = 0.576; 95% CI = 0.461-0.672). This finding indicates that, for a given newborn, an increase in PIPP-R values is associated with an increase in NSCF values (Figure 3).

4 DISCUSSION

In this study, we showed significant changes in both PIPP-R scores and NSCF during ROP screening, reaffirming that this eye examination is a painful and stressful procedure. However, contrary to our hypothesis, we did not demonstrate a significant correlation between NSCF and PIPP-R, suggesting that these tools evaluate different but complementary aspects of neonatal pain responses.

Scheduled eye examinations have been essential for the reduction of visual impairment rates among ex-preterm infants. However, these examinations are performed through pharmacologically dilated pupils and usually involve the application of intense illumination, physical restraints and manipulation of the eye, all of which can be sources of pain. For this reason, a combination of non-pharmacological and pharmacological analgesic measures are currently used, although we know that these methods provide only partial pain relief.[5,6,19] This phenomenon was observed in our sample, where in spite of different pain relief measures used, both PIPP-R scores and SC remained above the 'severe pain level', this is a PIPP-R > 12 or a NSCF > 0.44 peaks/sec.

Ideally, every analgesic measure should be accompanied by a reliable pain assessment, which can be especially challenging in non-verbal patients, such as neonates. In these situations, physiological and behavioural indicators, combined in clinical scales, are used as surrogates of self-report. There are over 40 scales to assess neonatal pain, but only a few have been validated in preterm infants; additionally, these scales are heterogeneous and provide an intermittent evaluation of pain. Therefore, the investigation of novel methods to detect pain is still an important line of research in neonatal medicine. In the 2016 AAP update on prevention and management of procedural pain in the newborn, SC was considered one of the promising and emerging technologies to assess pain, together with other autonomic measures, such as heart rate variability, and brain measures, such as near infrared spectroscopy or electroencephalography.[20]

Skin conductance is a method based on stress-induced sweating of the hand palms and foot soles. When an outgoing sympathetic nervous burst occurs to the skin, sweat glands are filled and SC increases until the gland is unfilled, creating an SC fluctuation that can be measured. One of the main advantages of SC is that it is objective, non-invasive, and can be monitored continuously.

There are two landmark studies regarding changes in SC during acute procedures, both performed in newborns during heel prick. These studies suggested that SC reflects the stress response of term and preterm neonates and proposed SC to be monitored as an indicator of pain.[7,8] More recently, Eriksson et al evaluated 27 full-term infants undergoing routine blood sampling.[9] These authors found that PIPP and the three SC variables (named *galvanic skin response*) increased more during painful stimulation than during tactile stimulation, concluding that SC is able to differentiate painful from nonpainful procedures.

The NSCF also showed a good correlation with the modified COMFORT sedation score during tracheal suction in mechanically ventilated children,[11] with ABC scale in full-term healthy newborns[21] and with subjective pain intensity among postoperative adult patients.[12] In contrast, and contrary to our hypothesis, we did not find a correlation between NSCF and PIPP-R during eye examination for ROP screening. However, both PIPP-R and NSCF increased significantly during the procedure, both peak at the time of scleral indentation (previously identified as the most painful component of ROP screening) and repeated measures correlation analyses showed moderate positive correlation. Therefore, we speculate that SC and PIPP-R simply evaluate different components of pain or stress responses. Similarly, PIPP-R was not correlated either with a novel pain measure based on heart rate variability in a prospective study of 29 newborns undergoing painful procedures.[22] In another study performed in 61 critical children, although NFSC also increased during invasive procedures, the authors concluded that SC is not more sensitive or faster than clinical scales.[23]

The interpretation of these data from a clinical standpoint is not easy. One can consider a particular scale as a standard reference for pain detection, but there are also limitations in clinical scales, including PIPP-R, which can preclude their utilisation as synonymous with pain or no pain. In fact, there is no original gold standard of pain assessment to establish the validity of any scale.[24] Behavioural components of PIPP-R and other scales are processed supraspinal

and interpreted by an observer, different from the skin conductance peaks per sec, which is a nociceptive spinal reflex and provides an objective value. It is also possible that facial expressions included in PIPP-R may not be reflective of pain for procedures that can be prolonged in several steps, such as ROP screening.[19] Moreover, PIPP-R also includes physiological assessments that were thought to be specific to neonatal pain, but they are not. In fact, these assessments are strongly influenced by circulatory instability and the severity of illness, different from the skin conductance peaks per sec, which has acetyl choline acting on muscarinic receptors and is not influenced by circulatory instability. It is true that SC has its own limitations as well. This method ultimately reflects an increased activity of the sympathetic nervous system. Therefore, every factor that influences sympathetic tone could potentially alter the SC values (anxiety, stress, inotropes, temperature, etc). SC data should therefore be interpreted according to the particular procedure to which the infant is exposed, that is, if a procedure is previously known to be potentially painful and it provokes acute changes in SC values, they are likely related to pain.

In any case, our aim was not to validate or invalidate one specific instrument for measuring pain but to explore different responses to pain and stress. For this reason, we also separately studied the behavioural and physiological components of PIPP-R. Interestingly, these two different parts of PIPP-R were not correlated at all and with NSCF.

The findings that physiological and behavioural pain responses are sometimes dissociated are previously well documented. Indeed, significant discordance between behavioural and autonomic reactivity to pain has also been described in premature neonates.[25] This idea is part of the rationale for the use of multidimensional scales but also raises doubts about the convenience of combining all these responses in a single score.

Interestingly, in a randomized controlled study aimed to evaluate the efficacy of oral sucrose and non-nutritive sucking during ROP screening, Dili et al observed significantly lower PIPP

scores in the intervention group, but without changes in physiological variables.[26] Similarly, Kabatas et al found a significant effect of oral paracetamol on PIPP scores but not in physiological parameters.[27]

These results confirm that joint interpretation of physiological and behavioural responses to pain is still a challenge. The relations between behavioural and autonomic reactivity to pain are likely complex, and some newborns could respond more physiologically and less behaviourally, or vice versa. Therefore, optimal pain management should require accurate and diversified pain assessment on an individual basis or even shift our focus to an easier and simple pain-detection method for routine care.[24]

There are some limitations to our study. First, we did not score the PIPP-R from video recordings, but performed this analysis in real time during the procedure, which can be more prone to subjectivity and bias. However, this score was calculated by two investigators who had gone specific training with the use of the scale, and our PIPP-R results are concordant with other published studies in the same context.[6] Second, we cannot exclude the fact that this scale, as many others, is imperfect. Nevertheless, it is considered a reliable measure of acute pain, and it is the outcome most used in pain intervention studies during ROP screening.[28] Third, it has been recommended that correlation tests such as ours should not be used to study pain by SC and instead cut-off values should be used to discover the level of pain.[28] We explored whether there were differences in NSCF among the neonates in our sample with the higher PIPP-R scores (>12 points), but there were no differences. Therefore, no cut-off values could be described to predict severe pain in this study.

In conclusion, our study shows that during eye examination for ROP screening, there is a significant increase in both PIPP-R scores and SC responses, reaffirming that this examination is still a painful and stressful procedure. Even if the SC is not correlated with currently validated pain scales, changes observed in NSCF during the procedure make it an interesting tool to be

further studied. More research is needed to explore the relationship between SC and other pain detection tools and to define the clinical applicability of SC to evaluate stress responses in neonates. Although we cannot extend our results to other procedures, in our opinion neither SC nor PIPP-R should be used as the sole method for pain assessment during acute procedures in newborns.

CONFLICT OF INTEREST

None declared.

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Table 1. Demographic and basal characteristics. N = 53

Sex	
Male, no. (%)	18 (56.3)
Female, no. (%)	14 (43.8)
GA (weeks)	
Mean ± SD	30.2 ± 1.2
Median (IQ)	30.2 (29-31)
Birthweight (grams)	
Mean ± SD	1255 ± 311.7
Median (IQ)	1240 (1022-1445)
GA at examination (weeks)	
Mean ± SD	35.5 ± 1.9
Median (IQ)	35.5 (32-40.7)
Weight at examination (grams)	
Mean ± SD	1875.9 ± 390.3
Median (IQ)	1870 (1600-2205)
Age at examination (days)	
Mean ± SD	40 ± 13.5
Median (IQ)	34 (30-47)
Age at first examination (days)	
Mean ± SD	32.2 ± 6
Median (IQ)	31 (29-34)
ROP grade	
No ROP no. (%)	27 (84.3)
I-II no. (%)	4 (12.5)
III no. (%)	1 (3.1)
IV no. (%)	0 (0)

Abbreviations: GA, gestational age; IQ, interquartile range; ROP, retinopathy of prematurity; SD, standard deviation.

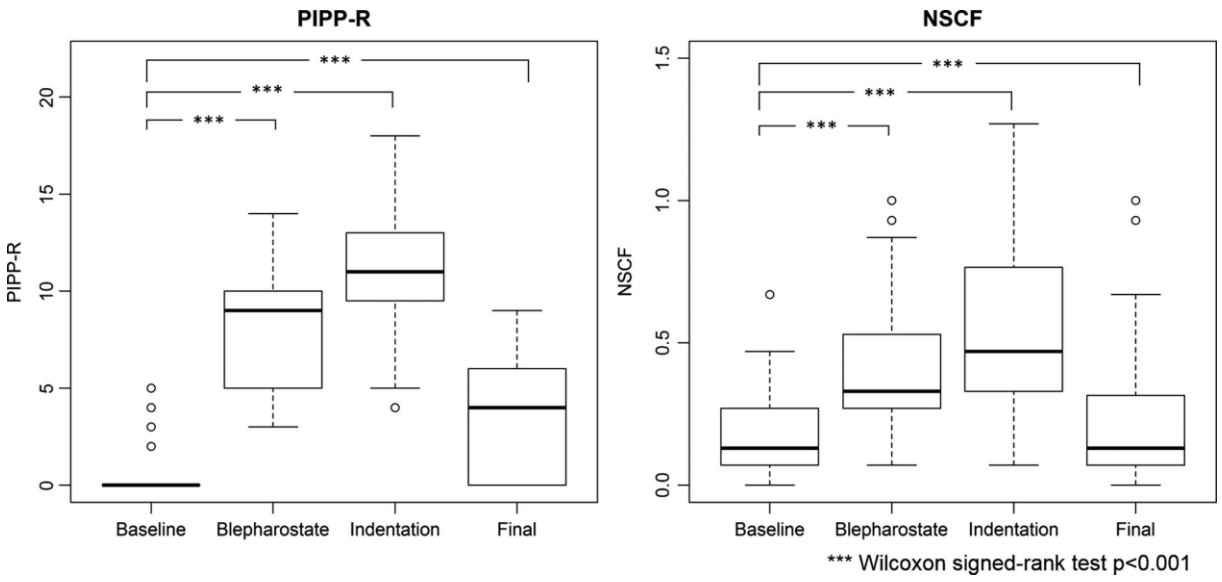

Figure 1. Box plot diagrams showing changes in Premature Infant Pain Profile-Revised (PIPP-R) and number of skin conductance fluctuations (NSCF) during the eye examination

Table 2. Correlation between the Premature Infant Pain Profile-Revised (PIPP-R) and number of skin conductance fluctuations (NSCF)

	Pearson's r		Spearman's rho	
	Correlation coefficient	*P*-value	Correlation coefficient	P-value
PIPPR-NSCF maximum	0.090	.520	0.06	.667
PIPPR-NSCF baseline	−0.040	.774	−0.071	.614
PIPPR-NSCF blepharostate	0.010	.941	0.106	.450
PIPPR-NSCF indentation	0.077	.586	0.035	.804
PIPPR-NSCF final	0.068	.630	0.076	.589
Only behavioural indicators				
PIPPR-NSCF maximum	0.028	.845	0.033	.812
PIPPR-NSCF blepharostate	0.049	.726	0.129	.356
PIPPR-NSCF indentation	0.049	.729	0.071	.614
Only physiological indicators				
PIPPR-NSCF maximum	0.023	.873	0.025	.859
PIPPR-NSCF blepharostate	−0.024	.867	0.012	.929
PIPPR-NSCF indentation	0.058	.678	0.075	.593

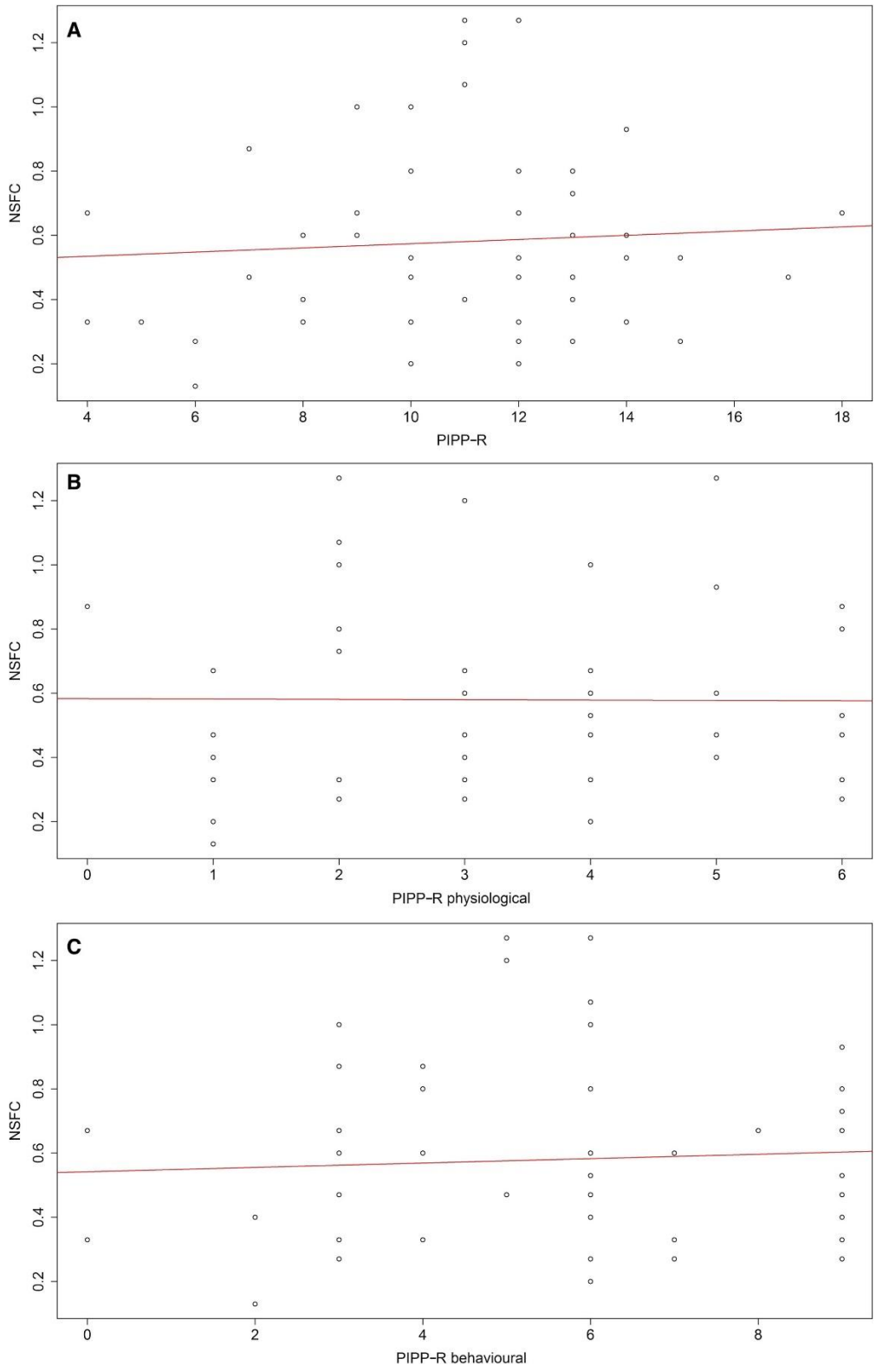

Figure 2. Correlation between maximum values of Premature Infant Pain Profile-Revised (PIPP-R) and number of skin conductance fluctuations (NSCF) during the eye examination. A), Correlation with the whole scale, (B) correlation only with physiological components of the scale and (C) correlation only with the behavioural components of the scale

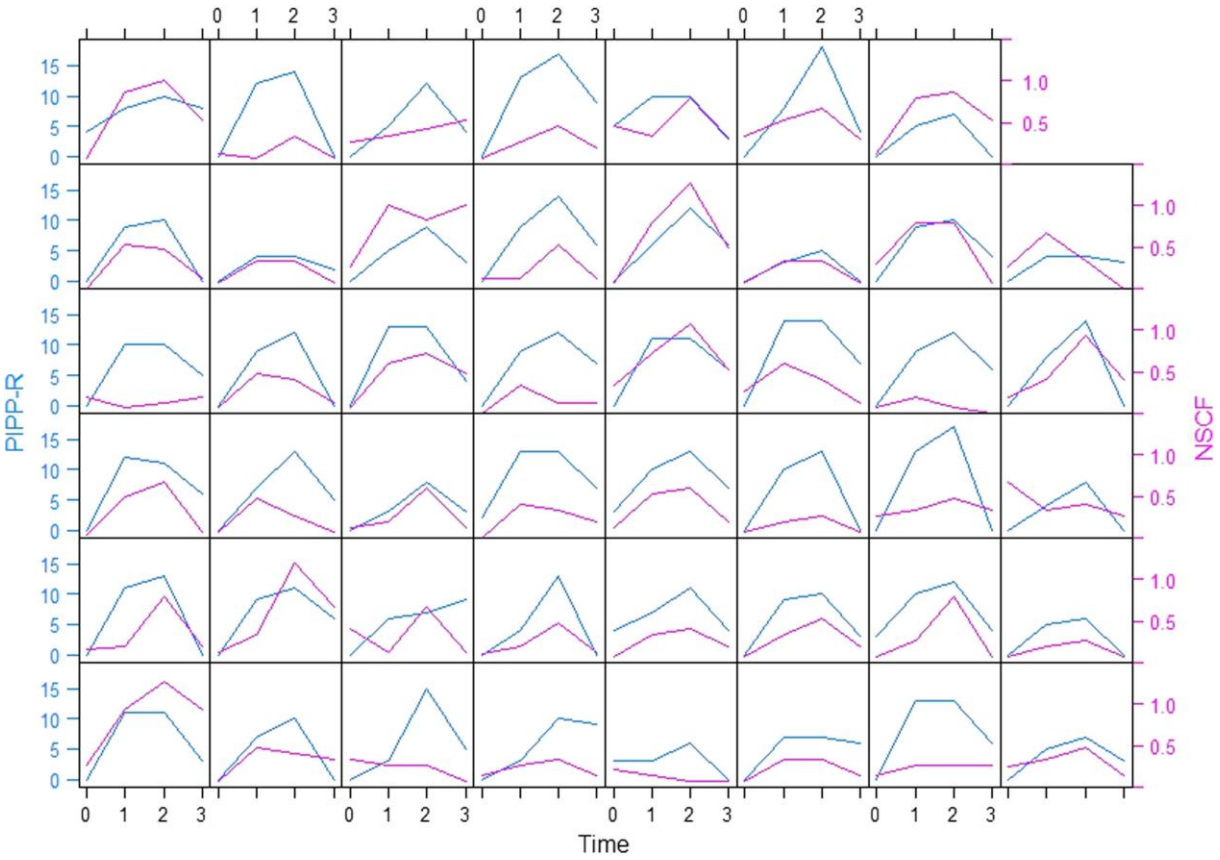

Figure 3. Changes in Premature Infant Pain Profile-Revised (PIPP-R) and number of skin conductance fluctuations (NSCF) during the eye examination. Every examination in the study is shown. Time 0 = baseline, time 1 = blepharostat, time 2 = indentation and time 3 = final