Somatosensory function and pain in extremely preterm young adults from the UK EPICure cohort: sex-dependent differences and impact of neonatal surgery

S. M. Walker¹,²,* A. Melbourne³, H. O’Reilly⁴, J. Beckmann⁴, Z. Eaton-Rosen³, S. Ourselin³ and N. Marlow⁴

¹Clinical Neurosciences (Pain Research), UCL Great Ormond Street Institute of Child Health, London, UK, ²Department of Anaesthesia and Pain Medicine, Great Ormond Street Hospital NHS Foundation Trust, London, UK, ³Translational Imaging Group, Department of Medical Physics and Biomedical Engineering, University College London, London, UK and ⁴Academic Neonatology, EGA UCL Institute for Women’s Health, London, UK

*Corresponding author. E-mail: suellen.walker@ucl.ac.uk

This article is accompanied by an editorial: Back To The Future: lifelong changes in pain processing in ‘ageing of prematurity’ by McCarthy & Colvin, Br J Anesth 2018;121:529–531, doi: 10.1016/j.bja.2018.06.017.

Abstract

Background: Surgery or multiple procedural interventions in extremely preterm neonates influence neurodevelopmental outcome and may be associated with long-term changes in somatosensory function or pain response.

Methods: This observational study recruited extremely preterm (EP, <26 weeks’ gestation; n=102, 60% female) and term-born controls (TC, n=48) aged 18–20 yr from the UK EPICure cohort. Thirty EP but no TC participants had neonatal surgery. Evaluation included: quantitative sensory testing (thenar eminence, chest wall); clinical pain history; questionnaires (intelligence quotient; pain catastrophising; anxiety); and structural brain imaging.

Results: Reduced thermal threshold sensitivity in EP vs TC participants persisted at age 18–20 yr. Sex-dependent effects varied with stimulus intensity and were enhanced by neonatal surgery, with reduced threshold sensitivity in EP surgery males but increased sensitivity to prolonged noxious cold in EP surgery females (P<0.01). Sex-dependent differences in thermal sensitivity correlated with smaller amygdala volume (P<0.05) but not current intelligence quotient. While generalised decreased sensitivity encompassed mechanical and thermal modalities in EP surgery males, a mixed pattern of sensory loss and sensory gain persisted adjacent to neonatal scars in males and females. More EP participants reported moderate–severe recurrent pain (22/101 vs 4/48; χ²=0.04) and increased pain intensity correlated with higher anxiety and pain catastrophising.

Conclusions: After preterm birth and neonatal surgery, different patterns of generalised and local scar-related alterations in somatosensory function persist into early adulthood. Sex-dependent changes in generalised sensitivity may reflect...
Preterm birth is an acknowledged health care priority because of its increasing prevalence, acute morbidity, and persistent impact on multiple health outcomes. Exposure to repeated painful procedures and surgical interventions during neonatal intensive care, particularly after extreme preterm birth (<28 weeks gestation), is occurring at a time when the developing nervous system is vulnerable to altered levels of activity. Improved recognition of pain is a research priority for neonates born preterm to guide management and minimise acute distress, but the longer-term impact of increased procedural pain exposure and neonatal surgery on brain structure and connectivity and adverse neurodevelopmental outcome is increasingly recognised. However, the degree to which biological effects associated with preterm birth persist into adulthood or are modulated by subsequent experience and psychosocial factors can vary.

Understanding effects of preterm birth and neonatal surgery on both somatosensory and affective components of pain response is necessary to identify factors that influence current pain experience, influence future risk, or both. Persistent alterations in somatosensory function have been demonstrated in preterm-born children, but may be influenced by the subsequent age- and sex-dependent changes in sensory thresholds throughout adolescence. Psychological factors that influence pain experience, such as increased anxiety persist into early adulthood after extreme preterm birth, and higher pain catastrophising was noted in preterm children. Reported associations between preterm birth and chronic pain prevalence vary, but the different methodologies and populations in epidemiological and cohort studies, and limited details about the type, severity, and impact of pain, hamper comparison across studies.

This observational cohort study compared somatosensory function and pain experience in extremely preterm-born (EP; <26 weeks gestation) and healthy term-born young adults. We hypothesised that group differences in thermal sensitivity and the added impact of neonatal surgery previously identified at 11 yr in this cohort would persist at 19 yr. In addition, we explored associations with neuroanatomical factors, current pain experience, cognitive function, anxiety, and pain catastrophising. As male sex is an independent risk factor for adverse neurodevelopmental outcome after preterm birth, and sex/gender influences experimental pain sensitivity and chronic pain prevalence in adulthood, outcomes were compared in males and females.

Methods

Participants

Participants were recruited from the UK EPICure population-based cohort of infants born extremely preterm in the UK and Ireland from March to December 1995. Although extreme preterm birth is defined as <28 weeks gestation, the EPICure cohort restricted recruitment to earlier high-risk births at <26 weeks gestation. Of 811 infants of the correct gestational age admitted to neonatal intensive care, 497 died in hospital and 314 were discharged home. Participation in longitudinal evaluation at 30 months, 6 yr, 11 yr, and at 19 yr has been previously described. The current study was approved by the National Research Ethics Committee Hampshire A (Reference: 13/SC/0514), described on the cohort website (EPICure@19; www.epicure.ac.uk), and potential participants received written information. Non-participants had previously asked not to be contacted, declined participation, or were uncontactable. EP participants in EPICure@19 did not differ in birth weight, gestational age, or sex from those lost to follow-up, but had higher mean full-scale intelligence quotient (FSIQ) scores at earlier assessments and higher socio-economic backgrounds than non-participants. After giving written consent, participants underwent a 2 day evaluation at the University College London Hospital, Clinical Research Facility (London, UK) between February 2014 and October 2015. Pain and somatosensory function were evaluated in 102 EP and 48 term-born control (TC) young adults (Fig. 1) in a dedicated sensory testing facility at University College London Great Ormond Street Institute of Child Health (London, UK). Additional data related to neonatal variables, participant characteristics, and questionnaires at 18–20 yr were extracted from the main EPICure database. Data related to conditioned pain modulation are reported in the companion manuscript (Walker and colleagues, Br J Anaesth in press). Reporting is in accordance with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) Checklist for cohort studies.

Assessments

A standardised clinical pain history included: site, intensity (0–10 verbal rating scale, VRS), frequency, and duration of recurrent pain; impact on function and activity; interference with usual activity due to recurrent pain (0–10 VRS); and analgesic use. Overall pain report was graded by a pain clinician (S.M.W.; 0–no regular pain, 1–infrequent pain, does not limit activities, 2–more frequent pain with some impact on function, 3–more severe pain that limits activity). Participants
used visual analogue scales (0–10 cm) to report current pain intensity (right now; average in the past week; worst pain in the past week), interference with usual activities because of pain, and anticipatory anxiety before testing.29

Quantitative sensory testing
Somatosensory function was assessed with a standardised protocol30,31 adapted to match previous preterm-born cohort studies.11,13 Evaluation was performed by a single investigator (S.M.W.) in the same temperature-controlled room with standardised verbal instructions. Before data acquisition, tests were demonstrated and participants advised they could decline or cease testing at any point. Testing was performed on the thenar eminence of the self-reported non-dominant hand to evaluate generalised thresholds and then on the chest wall. Localised testing adjacent to neonatal scars was restricted to thoracic dermatomes (high proportion of EP but no TC participants had chest scars when previously evaluated13). Participants without scars had testing on the lateral chest wall within the second to sixth thoracic dermatomes. Thermal thresholds were not obtained in two of 38 EP females because of equipment malfunction. The need to ask about prior surgery, and the site and nature of neonatal scars, precluded the investigator being blinded to group.

Modalities included: i) cool (CDT) and warm detection (WDT), cold (CPT) and heat (HPT) pain thresholds using a handheld 18 × 18 mm contact thermode (baseline 32°C, 1°C/s, limits 10°C and 50°C; Senselab MSA Thermal Stimulator; Somedic, Sodasa, Sweden) to match testing at 11 yr;13 ii) mechanical detection threshold (MDT) with von Frey hairs (geometric mean of 10 appearance and disappearance thresholds); iii) mechanical pricking pain threshold (MPT) with ascending PinPrick Stimulators (8–512 mN) until discomfort/pain rated 0–10 (VRS) then after 1 s−1 train of 10 repeated stimuli (VRS10) to calculate wind-up ratio (WUR=VRS10−VRS1);11 and iv) pressure pain threshold (PPT) mean of three values on middle phalanx of middle finger with hand-held 1 cm² algometer and optical feed-back (ramp 40 kPa s−1, maximum 1000 kPa; SENSEBox; Somedic, Sosdala, Sweden). As static thermal thresholds demonstrated reduced sensitivity in children after preterm birth, but a prolonged thermal stimulus unmasked increased sensitivity,11 cold pressor testing was also evaluated (see also conditioned pain modulation protocol; Walker et al.28 Br J Anaeth, in press). The hand was immersed to the wrist with the fingers spread into a 5°C circulating water bath (TE-10D Thermoregulator, B-8 Bath, RU-200 Dip Cooler; Techne, Burlington, VT, USA) and immersion duration (maximum 30 s) recorded.

Questionnaires
Self-report questionnaires (investigators H.O. and J.B.) included: i) Pain Catastrophizing Scale (PCS; total 0–52, subscales rumination, magnification, helplessness)32; ii) Diagnostic and Statistical Manual (DSM) anxiety t-score (range 50–100; ≥70 clinically significant) and internalising problems t-score (range 50–100; ≥64 clinically significant) extracted from Achenbach Adult Self-Report Questionnaire33; and iii) FSIQ using the Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II; mean: 100, SD: 15).34

MRI
We acquired 3D T1-weighted MPRAGE (TR/TE=6.93/3.14 ms) volumes at 1 mm isotropic resolution on a Philips 3T Achieva (Philips, Amsterdam, Netherlands) MRI scanner and carried out a multi-class tissue segmentation of the white matter volume using combined multi-atlas and Gaussian mixture model segmentation routines.35 This method produces a state-of-the-art segmentation and region labelling by voxel-wise voting between several propagated atlases guided by

Fig 1. EPICure recruitment and assessment flowchart. E@19, EPICure at 19 yr study; F, female; M, male; QST, quantitative sensory testing.
the local image similarity. This algorithm automatically estimates thalamus and amygdala volumes. See Supplementary material for pathway specific tissue properties (fractional anisotropy and average intra-axonal volume fractions).

Statistical analysis
As this descriptive cohort study aimed to recruit the maximum available subjects, no a priori power calculation was performed. Statistically significant group differences in thermal thresholds were found when 43 EP and 44 TC participants from the current cohort were tested at age 11 yr.13

Statistical analyses included: group-wise comparisons with Mann–Whitney U-test or two-tailed Student’s t-test; two-way ANOVA with group (TC, EP, EP+surgery) and sex as variables for normally-distributed or log-transformed mechanical data;14 two-sided χ² test for categorical data; two-tailed Spearman’s rho (rs) for bivariate correlations; and log rank Mantel–Cox for survival curves. Truncated regression models evaluated generalised thermal sensitivity [GTS: time to HPT, 32–50°C at 1°C s⁻¹] or [time to CPT, 32 to 10°C] (cold pressor duration) with higher values reflecting increased thermal tolerance (i.e. decreased sensitivity; maximum: 18–22 to 30–70). For quantitative sensory testing (QST) profiles, sex-matched Z-transformed scores were calculated as Z = (XEP participant – Meancontrols)/SDcontrols and adjusted so >0 indicates increased sensitivity and <0 decreased sensitivity.20 Analyses was performed with SPSS Version 23 (IBM, Portsmouth, UK) and Prism Version 7 (GraphPad, San Diego, CA, USA). P values are reported with Bonferroni adjustment for multiple comparisons.

Results

Participant characteristics
One hundred and two EP and 48 age- and sex-matched TC participants underwent pain and somatosensory assessment (Fig. 1). EP participants had lower height and weight, but the same BMI as TC (Table 1). FSIQ scores were lower in the EP group, but did not differ between QST and remaining EPICure@19 participants.32 Thirty EP participants had required neonatal surgery (12 closure patent ductus arteriosus, seven laparotomy, 10 inguinal hernia repairs, and one ventricular drain). The surgery subgroup had longer initial hospitalisation, but did not differ in birth weight, gestational age or risk index score on neonatal ICU (NICU) admission (Supplementary Table 1). QST results were excluded because of variability in three EP males (two had difficulty with numerical scales; one reported tiredness and difficulty concentrating). Chest wall testing was declined in three EP subjects (time; scar allodynia; tired), and one EP female with Rayaud’s symptoms declined cold evaluation (Fig. 1). No participant reported distress during testing.

Thermal thresholds and cold tolerance
Thenar eminence sensitivity for all thermal modalities (CDT, WDT, CPT, HPT) was reduced in the EP vs TC group (Fig. 2a; Supplementary Table 2). Consistent with previous group differences at 11 yr,13 median CPT was lower (−3.8°C, 95%CI −5 to −0.6°C, P<0.01) and HPT was higher (2.6°C 95%CI 0.2–3.6°C, P=0.03) in EP vs TC participants. This was on a background of age-related increase in threshold in both TC (median HPT at 19 vs 11 yr +4.4°C, 95%CI 2.6–5.9) and EP participants (+4.3°C, 95% CI 2.5–5.8; Supplementary Table 3). Within-subject sensitivity to heat and cold was inversely correlated in both TC (HPT and CPT: rs=−0.80, 95%CI −0.91 to −0.63, P<0.01) and EP participants (rs=−0.82, 95%CI −0.87 to −0.73, P<0.01).

When evaluating static thermal thresholds, more EP participants reached thermal test limits without experiencing discomfort/pain. Twenty-six (27%) EP and 2 (4%) TC had HPT >49°C, and 26 (27%) EP and 5 (10%) TC had CPT <11°C. Survival curves evaluated subgroup effects at the limits of testing (Fig. 2c–f), with failure to reach HPT or CPT most common in EP males with neonatal surgery. Raw data analyses also identify sex-dependent differences related to EP status and neonatal surgery (Supplementary Table 4).

In response to a more prolonged noxious cold stimulus, EP participants were more likely to withdraw the hand before 30 s of cold pressor testing (OR=2.2, 95%CI 1.1–4.4), particularly EP surgery females (Fig. 2g). In EP males, cold pressor tolerance did not differ from TC, and there was a relative left-shift compared with threshold survival curves. GTS provided a summary measure incorporating time to HPT and CPT and duration of cold pressor tolerance, with higher scores (range 0–70 s) representing reduced sensitivity. Truncated regression modelling identified significant interactions between EP surgery and sex (Supplementary Table 5), with decreased sensitivity in EP surgery males (69 s, 95%CI 53–85) but increased sensitivity in EP surgery females (39 s 95%CI 30–48; Fig. 2b).

Thermal sensitivity and amygdala volume
Imaging data were available for 39 TC and 72 EP QST participants, including 16 of 30 EP neonatal surgery participants. The volume of pain-relevant brain regions was influenced by preterm status, sex, or both (Fig. 3a and b; Supplementary Fig. 1), with significant correlations with thermal sensitivity for the thalamus and amygdala (Supplementary Table 6). Amygdala volume was lower in EP than TC participants, with a significant main effect of EP status (F1,111=50, P<0.01) and sex (F1,111=23, P<0.01). Amygdalothalamic tract fractional anisotropy differed between TC females and EP females, but there were no differences in axonal volume across groups (Supplementary Fig. 2) and no difference in tissue composition using T2 relaxometry has been reported in this cohort.37 Lower amygdala volume sex-dependently correlated with reduced thermal sensitivity (HPT, CPT, and cold pressor tolerance) in males, but increased sensitivity in females (Supplementary Table 6). In EP participants, amygdala volume was negatively correlated with HPT in males (rs=−0.43, P=0.03) but positively in females (rs=0.44, P<0.01; Fig. 3e). Adjusting for amygdala volume increased effect sizes in the GTS model. FSIQ was not a significant predictor and therefore excluded (Supplementary Table 5).

Thenar and chest wall sensory profiles
Differences from TC data are expressed as z-scores to illustrate sensory profiles across thermal and mechanical modalities (Fig. 4). Decreases in thermal mechanical detection (MDT) and pressure pain sensitivity (PPT) in EP males were statistically significant in the neonatal surgery subgroup (Fig. 4b; Supplementary Table 2). Sensory thresholds on the unscarred chest wall are consistent with thenar values (i.e. no difference in females, reduced sensitivity in males; Fig. 4c and d; Supplementary Table 7).
Table 1: Demographic data: group and sex differences. *Sample size for full group; for outcomes where data was not available for all participants, the number of participants (n=) is included below the result. †Obtained using Mann–Whitney U-test; ‡P values by two-sided z test; 1Female neonatal surgery: closure patent ductus arteriosus (PDA) n=8; laparotomy n=4; inguinal hernia repair, IH, n=1; 2Male neonatal surgery: IH n=9, laparotomy n=3; PDA n=2, PDA+IH, n=2; CSF drain n=1: mod/sev, moderate or severe; IQR, inter-quartile range; MSK, musculoskeletal pain; occas., occasional; PCS, Pain Catastrophizing Scale; Ach, Achenbach Scale; VAS, visual analogue scale 0–10 cm; VRS, verbal rating scale (0 = no pain; 10 = worst pain can imagine)

| Characteristic                      | EPI Cure cohort | Term control (n=48)* | Female Extremely preterm (n=61)* | P-value | Male Extremely preterm (n=41)* | Term control (n=19)* | P-value |
|------------------------------------|----------------|---------------------|---------------------------------|---------|--------------------------------|---------------------|---------|
| **Participant characteristics**    |                |                     |                                 |         |                                |                     |         |
| Age (yr), mean (range)             | 19.3 (18.4–20.5) | 19.2               | 19.3 (18.4–20.3)                | 0.29†   | 19.3                           | 19.2                | 0.45†   |
| Height (cm), mean (SD)             | 163 (9.5)       | 167 (8.9)           | 158 (6.5)                       | 0.02†   | 158.2                          | 172 (6.7)           | 0.052†  |
| Weight (kg), mean (SD)             | 62.8 (13.9)     | 67.8 (15.6)         | 67.0 (15.1)                     | 0.048†  | 67.0                           | 69.8 (14.2)         | 0.31†   |
| Body mass index (kg m⁻²), mean (SD)| 23.4 (4.5)      | 24.1 (4.7)          | 23.2 (4.2)                      | 0.35†   | 23.2                           | 23.7 (5.0)          | 0.73†   |
| Male sex, n (%)                    | 40 (60)         | 19 (60)             | 19 (60)                         | 0.94‡   | 19 (60)                        | 21 (60)             | 0.61‡   |
| **Prior surgery**                  |                |                     |                                 |         |                                |                     |         |
| Neonatal/initial admission, n (%)  | 30 (29)         | 0 (0)               | 13 (21)                         | <0.01§  | 17 (41)                        | 0 (0)               | <0.01§  |
| Subsequent surgery, n/N (%)        | 41/93 (44)      | 15/46 (33)          | 9/27 (33)                       | 0.9†    | 15/38 (30)                     | 6/19 (32)           | 0.77†   |
| **Pain history**                   |                |                     |                                 |         |                                |                     |         |
| Intensity worst pain in past week VAS, median (IQR) | 2.7 (0–5) | 1.4 (0–4.5) | 2.1 (0–6) | 0.66† | 2.1 (1–6) | 1.3 (0–5) | 0.80† |
| Incidence recurrent pain, %, (n/N) | 54 (55/101)     | 58 (58/58)          | 56 (56/56)                      | 0.31†   | 56 (56/56)                     | 56 (56/56)          | 0.32†   |
| Primary pain site, %               |                |                     |                                 |         |                                |                     |         |
| Pain ranking, %                    |                | no/mild             | no/mild                         | 0.34‡   | no/mild                        | no/mild             | 0.34‡   |
| Recurrent pain intensity VRS, mean (SD) | 6.2 (2.6) | 5.7 (2.5) | 6.3 (2.8) | 0.65† | 6.3 (2.8) | 5.8 (2.5) | 0.88† |
| Interference because of pain VRS, mean (SD) | 3.3 (3.8) | 1.4 (2.6) | 3.3 (4.1) | 0.02† | 1.3 (2.3) | 1.2 (2.2) | 0.03† |
| Analgesia use, %                   |                | none                | none                            | 0.40†   | none                           | none                | 0.40†   |
| Questionnaires                     |                |                     |                                 |         |                                |                     |         |
| PCS total score, median (IQR), n   | 5 (5–14)        | 5 (0–14)            | 7 (1–16)                        | 0.53†   | 7 (1–16)                       | 6.5 (0–19)          | 0.93†   |
| DSM anxiety T score Ach, median (IQR), n | 52 (50–58) | 50 (50–54) | 52 (50–60) | 0.01† | 52 (50–54) | 50 (50–54) | 0.10† |
| Full-scale intelligence quotient score, mean (SD) | 87.2 (14.9) | 103.8 (10.1) | 89.2 (14.5) | <0.01† | 89.2 (14.5) | 102 (8.1) | <0.001† |
Localised sensory change adjacent to neonatal scars

Testing on the unscarred lateral chest wall was performed in all TC and 63 EP participants. Thirty-three EP participants (22 female, 11 male) had clearly visible thoracic dermatome scars related to open surgery (n=16) or surgical vascular access and chest drain insertion (n=11). Localised decreases in static thermal and mechanical detection thresholds adjacent to neonatal thoracic scars were apparent in EP females (Fig. 4c) but were more marked and on a background of generalised differences in EP males (Fig. 4d). Mechanical detection threshold (MDT) was higher on the chest than the hand (Supplementary Tables 4 and 7), with good correlation between the sites (\( r_s = 0.67 \) for TC; \( r_s = 0.68 \) for EP). Normalised data show a main effect of group (TC vs EP vs EP+surg; \( F_{2,135} = 13, P<0.01 \)), but not sex (\( F_{1,135} = 0.5, P = 0.5 \), with thresholds
adjacent to scars higher than TC in both females and males (Supplementary Table 7). This is consistent with the scar-related localised decrease in static mechanical and thermal sensitivity in this cohort at 11 yr. A small number of participants in all groups reported either rapid change in perceived thermal intensity (TC vs EP vs EP + scar: 6/48 vs 13/61 vs 10/33) or paradoxical hot/cold sensations (TC vs EP vs EP + scar: 4/48 vs 10/61 vs 4/33).

Mechanical perceptual sensitisation (positive wind-up ratio) was more common adjacent to scars [23/31, 75% vs unscarred EP (31/63, 49%) or TC (19/48, 40%); $\chi^2$ P < 0.01]. Alloodynia to brush (DMA rated as VRS 2–10/10) was reported over thoracic (8/31 EP) and other neonatal scars (additional four EP participants VRS 2–6/10; Fig 4c and d). Within the surgery subgroup, higher scar-related brush alldynia correlated with a lower GTS score (i.e. increased sensitivity; $r_s = -0.49$, P < 0.05). Three EP participants declined testing adjacent to scars because of persistent sensitivity. No participants reported brush allodynia on the unscarred chest wall or thenar eminence.

**Cognitive function and sensory thresholds**

There was a significant effect of group on FSIQ score (TC, EP, EP + surgery; $F_{2,344} = 32; P < 0.01$), but no main effect of sex ($F_{1,344} = 0.09; P = 0.81$). Neonatal surgery had a similar added effect in both males (EP vs EP + surgery, 87.4, 13.6 vs 79.6, 16.1; mean, sd) and females (EP vs EP + surgery, 91.3, 14.5 vs 81.1, 12.3). Lower FSIQ correlated with lower brain region volumes in both males and females, but not with sensory thresholds (Supplementary Table 6).

**Current pain, pain catastrophising, and anxiety**

Regular pain was common, particularly mild musculoskeletal pain related to work or sporting activity. Moderate-severe pain requiring analgesia or impairing function was more common in EP (22/101; 22%) than TC (4/48; 8%) participants ($\chi^2$ P = 0.04). For those with regular pain, self-reported interference with activity because of pain was higher in EP participants (Table 1). Higher anxiety and pain catastrophising scores correlated weakly with thermal pain thresholds and more strongly with increased pain severity in EP participants (Supplementary Table 8).

No participants had taken analgesia on the test day. More females than males reported headache (26/89; 29% vs 6/60; 10%) and use of analgesia (32% vs 13%), but these outcomes were not influenced by EP status. Prevalence data exclude menstruation pain as many did not spontaneously report this or were taking hormone treatment for symptom management.

![Fig 3. Amygdala volume and thermal sensitivity.](image)
or contraception. In those specifically asked, the mean intensity of period pain was 7.1, 2.3 (VRS 0–10; mean, SD) with 12/30 EP and 5/18 TC females reporting problematic pain that reduced activity.

After demonstration of sensory tests, pretest anxiety was low and did not correlate with thermal thresholds (Supplementary Table 8). DSM anxiety scores were higher in EP participants (Table 1) with clinically significant scores ≥70 in one of 38 EP males, five of 57 EP females, and two of 28 TC females. All pain catastrophising subscales had high internal consistency (Cronbach’s α=0.8) in TC (0.91; subscales 0.81–0.92) and EP (0.91; subscales 0.82–0.91) participants. Overall, pain catastrophising scores were influenced by female sex (P=0.028), and current pain experience (HUI-3 pain score; F=0.032), but not EP status or FSIQ.

**Discussion**

This is the first comprehensive evaluation of sex- and modality-dependent somatosensory function in young adults who had been born extremely preterm. Sensitivity to static thermal thresholds was reduced in EP males, but prolonged noxious cold unmasked increased sensitivity in EP females, with the greatest difference in neonatal surgery subgroups. The degree and sex-dependent directionality of altered thermal sensitivity in EP participants correlated with reduced amygdala volume but not with current cognitive function, suggesting the amygdala plays a sex-dependent role in central modulation of experimental pain stimuli. In contrast to these generalised changes, a mixed pattern of sensory loss and sensory gain was localised to neonatal scars in both males and females. EP participants were more likely to report current pain of at least moderate severity, with increased pain intensity also associated with higher anxiety and pain catastrophising scores.

Extremely preterm babies undergo repeated procedural interventions as part of intensive care management and up to a third require surgery to manage complications or congenital anomalies. Cumulative pain exposure is difficult to quantify and is confounded by comorbidity. Duration of mechanical ventilation or NICU stay have been used as proxy measures of pain exposure and higher numbers of tissue breaking procedures correlate with worse outcome. We used neonatal surgery as an indicator of increased tissue injury, although this may also be confounded by disease severity or

---

**Fig 4.** Somatosensory profiles on hand and chest. (a,b) Thenar sensory profiles in extremely preterm (EP) females (a) show minor differences in z-score (normalised to term controls, TC). (b) In EP males with neonatal surgery (EP+surg), differences from TC extend across thermal and mechanical modalities. (c,d) Adjacent to neonatal thoracic scars (EP+scar), minor differences in warm and mechanical detection are seen in females (c) but in EP males there are generalised reductions in threshold sensitivity on the chest wall that are more marked in the EP+s-scar group (d). Scar-related perceptual sensitisation (positive wind-up ratio) and dynamic mechanical allodynia (DMA; numerical rating scale, NRS 0–10) to brush is observed in females (neonatal scars on chest wall or other body sites) and males. Data = z-score mean (95%CI) with increased sensitivity represented as positive and decreased sensitivity as negative values. EP vs TC: †P<0.05 ‡P<0.01; EP+surgery or EP+scar vs TC: †P<0.05 *P<0.01.
peroperative instability, and specific effects of analgesia or anaesthesia cannot be determined from the available data. As also seen here, surgery during initial hospitalisation has a persistent impact on cognitive outcome. However, FSIQ scores did not differ between our male and female EP surgical participants, and do not account for differences in the degree or directionality of altered thermal sensitivity in males and females.

Temperature detection is mediated by multiple thermosensitive channels responsive to both stimulus intensity and duration. In children born very preterm (VP, <32 weeks gestation) thermal threshold sensitivity was no different or decreased. Our EP participants were born at an earlier gestational age (24.9, 0.8 weeks; mean, sd) and required longer hospital admission (134, 63 days), and the reduced thermal threshold sensitivity and added impact of neonatal surgery noted at 11 yr had persisted. This was on a background of expected age-related increase in threshold, but clear sex-dependent differences had now emerged. The individual variability in thermal pain thresholds is consistent with previous reports, but within-subject consistencies included: discrimination of stimulus intensity (heat at higher temperature than warm, cold lower temperature than cool); reduced sensitivity to both hot and cold; and correlations across different body sites. In contrast to these measures of static thermal thresholds, more prolonged and noxious thermal stimuli activate descending modulatory pathways that can shift the balance between inhibition or facilitation of spinal inputs and influence perceived pain intensity. Therefore, in addition to measures of static thermal threshold, we also performed cold pressor testing to assess sensitivity to a more prolonged and intense thermal stimulus. Previously, VP children were shown to have reduced threshold sensitivity, but prolonged heat unmasked increased perceptual sensitisation and increased activation in pain-relevant brain regions, including primary somatosensory cortex, thalamus, and basal ganglia. Reduced cold pressor tolerance has also been previously reported in EP young adults. Routine QST profiles do not include prolonged thermal stimuli, but a composite measure including time to thermal thresholds and cold tolerance (GTS) highlighted decreased sensitivity in EP males, increased sensitivity in EP females, and the added impact of neonatal surgery in both. We postulate that increased tissue injury and pain in early life contributes to activity-dependent alterations in thermal nociceptive signalling, that are also influenced by sex-dependent differences in central modulation.

Experimental pain sensitivity has been correlated with altered structure and connectivity in central sensory-discriminative (e.g. thermal sensitivity and somatosensory cortical thickness) and emotional/affective pathways (e.g. visceral sensitivity and thalamus and amygdala volume), with sex differences in fMRI response predominantly in regions encoding affective pain response. In EP participants, thermal sensitivity correlated with amygdala volume. The amygdala attaches emotional significance to sensory information relayed from the thalamus, and altered amygdala connectivity has been associated with pain-related fear in adolescents and pain catastrophising in adults. Importantly for evaluation of future risk, alterations in amygdala volume and connectivity also predicted the transition from acute to chronic back pain in adults. After preterm birth, alterations in brain structure and connectivity persist beyond adolescence, and functional correlates include reduced cognitive ability and poorer psychosocial functioning. More specifically, differences in amygdala volume and connectivity influenced fear processing and emotion recognition after preterm birth. Here, amygdala volume correlated with both the degree and directionality of altered thermal sensitivity (i.e. decreased in males, increased in females). As sex-dependent differences in amygdala activation also emerge during adolescence, divergence in thermal sensitivity between males and females may be clearer in early adulthood than at younger ages. Alterations in socio-emotional circuits, which are influenced by biological vulnerability, early life adversity, and parenting, have been proposed as a link between preterm birth and subsequent psychosocial and emotional outcomes, and we suggest extending this model to include effects on experimental pain sensitivity in EP young adults. These exploratory associations require further evaluation in functional imaging studies.

Neonatal scars were associated with decreased static thresholds but increased dynamic mechanical sensitivity in both males and females, suggesting a different localised effect related to peripheral tissue injury. Comparison across multiple modalities is facilitated by conversion to z-scores, and differences from large reference control datasets identify specific sensory profiles in adults with peripheral neuropathic pain. Here, we restricted comparison to contemporaneous age- and sex-matched controls and used a protocol that facilitated comparison with previous preterm cohorts. Despite the relatively small subgroups and limited effect size for some modalities, the sensory profiles illustrate sex-dependent effects, the added impact of neonatal surgery, and a different pattern of generalised and localised sensory change adjacent to neonatal scars. Similar mixed patterns of sensory gain, loss, or both have been reported after inguinal or thoracic surgery in children and adults. While scar-related sensory changes do not always correlate with reported pain, several EP participants had marked brush allodynia or declined testing because of scar-related sensitivity, which may predispose to increased pain after re-injury. Repeat surgery in the same dermatome as prior neonatal surgery increased pain scores and analgesic requirements in infants. Our laboratory studies in rodents identified long-term alterations after neonatal hindpaw incision that include enhanced re-incision hyperalgesia in adulthood. Importantly, prevention by peri-incision local anaesthetic suggests activity-dependent mechanisms that can be modulated by clinically-relevant analgesic interventions. Although UK paediatric anaesthetists in 1995 reported regular use of opioids and local anaesthetic techniques for neonates requiring surgery, specific data for preterm neonates and this cohort are not available. Additional clinical studies are required to compare the ability of different systemic or regional analgesic techniques to modulate the long-term impact of neonatal surgery.

Pain is a complex sensory and emotional experience, requiring a biopsychosocial approach to evaluation and management. Psychosocial comorbidities are common and are effective targets for intervention in adolescents and adults with chronic pain. While some psychosocial factors can increase resilience or be protective (e.g. social support, active coping), others (e.g. fear of pain, anxiety, catastrophising) increase vulnerability and contribute to sex differences in experimental pain sensitivity. After preterm birth, children reported higher pain catastrophising, and increased anxiety persists into early adulthood. Here, higher anxiety and catastrophising scores in EP young adults correlated with both increased thermal sensitivity and more intense current pain.
Detailed pain phenotyping, which incorporates history, QST, anxiety, and pain catastrophising has been suggested for clinical trials, and along with neuroimaging, may enhance prediction of persistent pain risk and improve personalised pain management.

Epidemiological studies associate early life adversity and childhood somatic symptoms with increased risk of chronic pain in adulthood. Preterm birth (<37 weeks gestation) in 1958 had a minor impact on prevalence of widespread pain at 45 yr, EP survivors now reaching adulthood had more invasive NICU management at much earlier gestational ages. Longitudinal evaluations in extreme preterm cohorts have identified persistent effects on cognitive, mental health and system-specific health outcomes, but pain experience is not consistently reported. Based on quality of life or general health care questionnaires, current pain prevalence in VP or EP young adults has been reported as no different, decreased, or increased. Here, we found no difference in overall prevalence, as mild pain was common and the study was not adequately powered for this outcome. However, an increased proportion of EP participants reported moderate–severe recurrent pain that required analgesia and influenced activity. In VP and very low birth weight cohorts, self-reported pain increased throughout the third decade when chronic pain generally becomes more prevalent, particularly in women. Psychological interventions that encourage adaptive coping and improve self-management of pain have been suggested for preterm-born adults, and may be particularly advantageous if high-risk subgroups can be identified, such as females with both altered pain coping style and enhanced sensitivity to noxious stimuli. Standardised use of outcomes that incorporate type of pain, impact on function, and use of health resources by males and females would facilitate comparison across cohorts and more clearly delineate the impact of differing neonatal exposures and preterm birth on subsequent pain experience.

Study limitations include potential selection bias as not all eligible EPICure subjects attended. As long-term follow-up tends to recruit NICU survivors with a relatively favourable outcome and EPICure@19 participants had higher mean FSIQ and socioeconomic status than non-participants, results may under-estimate overall effects. Some participants did not complete all tests, either because of participant preference, time or test availability, but sample sizes for analyses based on available data are noted. Only half of the neonatal surgery group underwent MRI, which limited the ability to analyse subgroup effects for this outcome. Fewer EP males were tested but with a matched proportion of controls. The vast majority of subjects were Caucasian and differences related to ethnicity were not assessed. As subjects were not asked to self-report gender, dichotomous sex-differences are reported for males and females.

Extreme preterm birth affects 0.5–1% of the population and in the post-surfactant era more survivors are now reaching adulthood. For this vulnerable group, even modest increases in risk for future illness may represent significant healthcare burdens. Understanding persistent biological changes in nociceptive pathways and the psychosocial factors that modulate the risk and impact of persistent pain in later life will enhance awareness and recognition of targets for intervention to improve outcome throughout the lifespan. Early life experience and sex should be considered during clinical evaluations of somatosensory function or chronic pain, and when evaluating risk factors for persistent pain.

Authors’ contributions

Study design/planning: S.M.W., S.O., N.M.
Study conduct and data acquisition: S.M.W., A.M., H.O’R., J.B., Z.E.-R.
Data analysis: S.M.W., H.O’R., A.M.
Writing paper: S.M.W. with review: N.M.
Review and approval of final manuscript: all authors.
Overall planning and conduct of evaluations: EPICure@19 Study Group.

Acknowledgements

The authors and EPICure Study Group gratefully acknowledge the contribution of all participants and their families to the current and previous evaluations in this cohort. We also acknowledge the important contributions of all researchers and administrative staff involved in the EPICure@19 study and, in particular, assistance with statistical analysis by Kate Bennett. The EPICure@19 Study Group Investigators include: Neil Marlow, EGA UCL Institute for Women’s Health (Principal Investigator); John Cockcroft, Cardiff University; Xavier Golay, UCL Institute of Neurology; John Hurst, UCL; Samantha Johnson, University of Leicester; Sebastien Ourselin, UCL; Suellen Walker, UCL GOS Institute of Child Health; Dieter Wolke, University of Warwick.

Declaration of interest

The authors declare that they have no conflicts of interest.

Funding

Medical Research Council, UK (G0401525 to N.M., EPICure@19 Study Group). Department of Health, National Institute for Health Research Biomedical Research Centre funding scheme at University College London Hospital/University College London (part-funding to N.M.). Great Ormond Street Hospital Children’s Charity (Projects V2818 and W1071H to S.W.).

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.03.035.

References

1. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012; 379: 2162–72
2. Raju TNK, Buist AS, Blaisdell CJ, Moxey-Mims M, Saigal S. Adults born preterm: a review of general health and system-specific outcomes. Acta Paediatr 2017; 106: 1409–37
3. Walker SM. Translational studies identify long-term impact of prior neonatal pain experience. Pain 2017; 158(Suppl 1): S29–42
4. Duley L, Uhm S, Oliver S. Preterm birth priority setting partnership steering G. Top 15 UK research priorities for preterm birth. Lancet 2014; 383: 2041–2
5. Ranger M, Grunau RE. Early repetitive pain in preterm infants in relation to the developing brain. Pain Manag 2014; 4: 57–67
6. Duerden EG, Grunau RE, Guo T, et al. Early procedural pain is associated with regionally-specific alterations in thalamic development in preterm neonates. J Neurosci 2018; 38: 878–86
7. Stolwijk IJ, Keunen K, de Vries LS, et al. Neonatal surgery for noncardiac congenital anomalies: neonates at risk of brain injury. J Pediatr 2017; 182: 335–41 e1
8. Doyle LW, Cheong JL, Burnett A, et al. Biological and social influences on outcomes of extreme-preterm/low-birth weight adolescents. Pediatrics 2015; 136: e1513–20
9. Vinalli J, Miller SP, Bjornson BH, et al. Invasive procedures in preterm children: brain and cognitive development at school age. Pediatrics 2014; 133: 412–21
10. Vinalli J, Grunau RE. Impact of repeated procedural pain-related stress in infants born very preterm. Pediatr Res 2014; 75: 584–7
11. Hermann C, Hohmeister J, Demirakca S, Zohsel K, Flor H. Long-term alteration of pain sensitivity in school-aged children with early pain experiences. Pain 2006; 125: 278–85
12. Hohmeister J, Demirakca S, Zohsel K, Flor H, Hermann C. Responses to pain in school-aged children with experience in a neonatal intensive care unit: cognitive aspects and maternal influences. Eur J Pain 2009; 15: 94–101
13. Walker SM, Franck LS, Fitzgerald M, Myles J, Stocks J, Marlow N. Long-term impact of neonatal intensive care and surgery on somatosensory perception in children born extremely preterm. Pain 2009; 141: 79–87
14. Blankenburg M, Meyer D, Hirschfeld G, et al. Developmental and sex differences in somatosensory perception—a systematic comparison of 7- versus 14-year-olds using quantitative sensory testing. Pain 2011; 152: 2625–31
15. Boerner KE, Birnie KA, Caes L, Schinkel M, Chambers CT. Sex differences in experimental pain among healthy children: a systematic review and meta-analysis. Pain 2014; 155: 983–93
16. Pyhala R, Wolford E, Kautiainen H, et al. Self-reported mental health problems among adults born preterm: a meta-analysis. Pediatrics 2017; 139. e20162690
17. Lund LK, Vik T, Lydersen S, et al. Mental health, quality of life and social relations in young adults born with low birth weight. Health Qual Life Outcomes 2012; 10: 146
18. van Lunenburg A, van der Pal SM, van Dommelen P, van der Pal-de Bruin KM, Bennebroek Gravenhorst J, Verrips GH. Changes in quality of life into adulthood after very preterm birth and/or very low birth weight in The Netherlands. Health Qual Life Outcomes 2013; 11: 51
19. Roberts G, Burnett AC, Lee KJ, et al. Quality of life at age 18 years after extremely preterm birth in the post-surfactant era. J Pediatr 2015; 163. 1008–13.e1
20. Iversen JM, Indredavik MS, Evensen KA, Romundstad PR, Rygg M. Self-reported chronic pain in young adults with a low birth weight. Clin J Pain 2017; 33: 348–55
21. Rysavy MA, Marlow N, Doyle LW, et al. Reporting outcomes of extremely preterm births. Pediatrics 2016; 138: e20160689
22. Linsell L, Johnson S, Wolke D, et al. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: a prospective, population-based cohort study. Arch Dis Child 2018; 103: 363–70
23. Mogil JS. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. Nat Rev Neurosci 2012; 13: 859–66
24. Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. Pain 2017; 158(Suppl 1): S11–8
25. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. N Engl J Med 2000; 343: 378–84
26. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005; 352: 9–19
27. Johnson S, Fawke J, Hennessy E, et al. Neurodevelopmental disability through 11 years of age in children born before 26 weeks of gestation. Pediatrics 2009; 124: e249–57
28. Walker SM, O’Reilly H, Beckmann J, Marlow N. EPICure@ Study Group. Conditioned pain modulation identifies altered sensitivity in extremely preterm young adult males and females. Br J Anaesth 2018; 121: 636–46
29. Tsao JC, Seidman LC, Evans S, Lung KC, Zeltzer LK, Naliboff BD. Conditioned pain modulation in children and adolescents: effects of sex and age. J Pain 2013; 14: 558–67
30. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006; 123: 231–43
31. Blankenburg M, Boekens H, Hechler T, et al. Reference values for quantitative sensory testing in children and adolescents: developmental and gender differences of somatosensory perception. Pain 2010; 149: 76–88
32. Sullivan MJL, Bishop SR, Pavik J. The pain catastrophizing scale: development and validation. Psychol Assess 1995; 7: 524–32
33. Achenbach TM. Manual for the youth self-report and 1991 profile. Burlington, VT: University of Vermont; 1991
34. Wechsler D. Wechsler abbreviated scale of intelligence. 2nd ed. Bloomingon, MN: Pearson; 2011
35. Cardoso MJ, Modat M, Wolz R, et al. Geodesic information flows: spatially-variant graphs and their application to segmentation and fusion. IEEE Trans Med Imaging 2015; 34: 1976–88
36. Hirschfeld G, Zernikow B, Kraemer N, et al. Development of somatosensory perception in children: a longitudinal QST-study. Neuropediatrics 2012; 43: 10–6
37. Dingwall N, Chalk A, Martin TI, et al. T2 relaxometry in the extremely-preterm brain at adolescence. Magn Reson Imaging 2015; 34: 508–14
38. Courtois E, Droutman S, Magny JF, et al. Epidemiology and neonatal pain management of heelsticks in intensive care units: EPIPPAIN 2, a prospective observational study. Int J Nurs Stud 2016; 59: 79–88
39. Goffaux P, Lafrenaye S, Morin M, Patural H, Demers G, Marchand S. Preterm births: can neonatal pain alter the development of endogenous gating systems? Eur J Pain 2008; 12: 945–51
40. Vederhus BJ, Eide GE, Natvig GK, Markestad T, Graue M, Halvorsen T. Pain tolerance and pain perception in adolescents born extremely preterm. J Pain 2012; 13: 978–87
41. Marlow N. Anesthesia and long-term outcomes after neonatal intensive care. Paediatr Anaesth 2014; 24: 60–7
42. Soriano SG, Vutskits L, Jevtovic-Todorovic V, Hemmings HC. Neurotoxicology. Br J Anaesth 2017; 119: 443–7
43. Brenner DS, Golden JP, Vogt SK, Dhaka A, Story GM, Ger-eau Iv RW. A dynamic set point for thermal adaptation requires phospholipase C-mediated regulation of TRPM8 in vivo. Pain 2014; 155: 2124–33
44. Valkenburg AJ, van den Bosch GE, de Graaf J, et al. Long-term effects of neonatal morphine infusion on pain sensitivity: follow-up of a randomized controlled trial. J Pain 2015; 16: 926–33
45. Cruz-Almeida Y, Naugle KM, Vierck CJ, Fillingim RB, Riley JL. Reliability of pain intensity clamping using response-dependent thermal stimulation in healthy volunteers. BMC Neurosci 2015; 16: 21
46. Hohmeister J, Kroll A, Wollgarten-Hadamek I, et al. Cerebral processing of pain in school-aged children with neonatal nociceptive input: an exploratory fMRI study. Pain 2010; 150: 257–67
47. Erpelding N, Moayed M, Davis KD. Cortical thickness correlates of pain and temperature sensitivity. Pain 2012; 153: 1602–9
48. Elenbruch S, Schmid J, Kullmann JS, et al. Visceral sensitivity correlates with decreased regional gray matter volume in healthy volunteers: a voxel-based morphometry study. Pain 2014; 155: 244–9
49. Henderson LA, Gandevia SC, Macefield VG. Gender differences in brain activity evoked by muscle and cutaneous pain: a retrospective study of single-trial fMRI data. Neuroimage 2008; 39: 1867–76
50. Simons LE, Erpelding N, Hernandez JM, et al. Fear and reward circuit alterations in pediatric CRPS. Front Human Neurosci 2016; 9: 703
51. Jiang Y, Oathes D, Hush J, et al. Perturbed connectivity of the amygdala and its subregions with the central executive and default mode networks in chronic pain. Pain 2016; 157: 1970–8
52. Vachon-Presseau E, Tetreault P, Dhaka A, Story GM, Ger-eau Iv RW. A dynamic set point for thermal adaptation requires phospholipase C-mediated regulation of TRPM8 in vivo. Pain 2014; 155: 2124–33
53. Nozari C, Kowalik K, Vutskits L, et al. Prenatal stress alters amygdala functional connectivity in preterm neonates. Neuroimage Clin 2016; 12: 381–8
54. Hardee JE, Cope LM, Munier EC, Welsh RC, Zucker RA, Heitzeg MM. Sex differences in the development of emotion circuitry in adolescents at risk for substance abuse: a longitudinal fMRI study. Soc Cogn Affect Neurosci 2017; 12: 965–75
55. Faria V, Erpelding N, Lebel A, et al. The migraine brain in transition: girls vs boys. Pain 2015; 156: 2212–21
56. Baron R, Maier C, Attal N, et al. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. Pain 2017; 158: 261–72
57. Kristensen AD, Ahlburg P, Lauridsen MC, Jensen TS, Nikolajsen L. Chronic pain after inguinal hernia repair in children. Br J Anaesth 2012; 109: 603–8
58. Kristensen AD, Pedersen TA, Hjortdal VE, Jensen TS, Nikolajsen L. Chronic pain in adults after thoracotomy in childhood or youth. Br J Anaesth 2010; 104: 75–9
59. Werner MU, Ringsted TK, Kehlet H, Wildgaard K. Sensory testing in patients with postthoracotomy pain syndrome: Part 1: mirror-image sensory dysfunction. Clin J Pain 2015; 29: 775–83
60. Aasvang EK, Bransborg B, Jensen TS, Kehlet H. Heterogeneous sensory processing in persistent postherniotomy pain. Pain 2010; 150: 237–42
61. Wildgaard K, Ringsted TK, Hansen HJ, Petersen RH, Werner MU, Kehlet H. Quantitative sensory testing of persistent pain after video-assisted thoracic surgery lobectomy. Br J Anaesth 2012; 108: 126–33
62. Aasvang EK, Ringsted TK, Hansen HJ, Petersen RH, Werner MU, Kehlet H. Persistent sensory dysfunction in pain-free herniotomy. Acta Anaesthesiol Scand 2010; 54: 291–8
63. Aasvang EK, Gmaehle E, Hansen JB, et al. Predictive risk factors for persistent postherniotomy pain. Anesthesiology 2010; 112: 957–69
64. Peters JW, Schouw R, Anand KJ, van Dijk M, Duivenvoorden HJ, Tibboel D. Does neonatal surgery lead to increased pain sensitivity in later childhood? Pain 2005; 114: 444–54
65. Walker SM, Beggs S, Baccei ML. Persistent changes in peripheral and spinal nociceptive processing after early tissue injury. Exp Neurol 2016; 275: 253–60
66. Beggs S, Currie G, Salter MW, Fitzgerald M, Walker SM. Priming of adult pain responses by neonatal pain experience: maintenance by central neuroimmune activity. Brain 2012; 135: 404–17
67. Moriarty O, Harrington L, Beggs S, Walker SM. Opioid analgesia and the somatosensory memory of neonatal surgical injury in the adult rat. Advance Access published on February 1 Br J Anaesth 2018; 121: 314–24
68. De Lima J, Lloyd-Thomas AR, Howard RF, Sumner E, Quinn TM. Infant and neonatal pain: anaesthetists’ perceptions and prescribing patterns. British Medical Journal 1996; 313: 787
69. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull 2007; 133: 581–624
70. Eccleston C, Palermo TM, Williams AC, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2014; 5: CD003968
71. Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev 2012; 11. CD007407
72. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The role of psychosocial processes in the
development and maintenance of chronic pain. J Pain 2016; 17: T70–92
78. Caes L, Fisher E, Clinch J, Tobias JH, Eccleston C. The role of pain-related anxiety in adolescents’ disability and social impairment: ALSPAC data. Eur J Pain 2015; 19: 842–51
79. Goffaux P, Michaud K, Gaudreau J, Chalaye P, Rainville P, Marchand S. Sex differences in perceived pain are affected by an anxious brain. Pain 2011; 152: 2065–73
80. Edwards RR, Dworkin RH, Turk DC, et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. Pain 2016; 157: 1851–71
81. Davis KD, Flor H, Greely HT, et al. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. Nat Rev Neurol 2017; 13: 624–38
82. Jones GT. Psychosocial vulnerability and early life adversity as risk factors for central sensitivity syndromes. Curr Rheumatol Rev 2016; 12: 140–53
83. Littlejohn C, Pang D, Power C, Macfarlane GJ, Jones GT. Is there an association between preterm birth or low birthweight and chronic widespread pain? Results from the 1958 Birth Cohort Study. Eur J Pain 2012; 16: 134–9
84. Raju TN, Pemberton VL, Saigal S, Blaisdell CJ, Moxey-Mims M, Buist S. Long-term healthcare outcomes of preterm birth: an executive summary of a conference sponsored by the National Institutes of Health. J Pediatr 2017; 181. 309–18.e1
85. Cooke RW. Health, lifestyle, and quality of life for young adults born very preterm. Arch Dis Child 2004; 89: 201–6
86. Dalziel SR, Lim VK, Lambert A, et al. Psychological functioning and health-related quality of life in adulthood after preterm birth. Dev Med Child Neurol 2007; 49: 597–602
87. Saigal S, Stoskopf B, Pinelli J, et al. Self-perceived health-related quality of life of former extremely low birth weight infants at young adulthood. Pediatrics 2006; 118: 1140–8
88. Verrips G, Brouwer L, Vogels T, et al. Long term follow-up of health-related quality of life in young adults born very preterm or with a very low birth weight. Health Qual Life Outcomes 2012; 10: 49
89. van Ganzewinkel CJ, Been JV, Dieleman JP, et al. Pain coping strategies: neonatal intensive care unit survivors in adolescence. Early Hum Dev 2016; 103: 27–32
90. Johnson S, Marlow N. Early and long-term outcome of infants born extremely preterm. Arch Dis Child 2017; 102: 97–102

Handling editor: L. Colvin