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Long-term consequences of early infant injury and trauma upon somatosensory processing

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Abstract

Long-term consequences of early infant injury upon somatosensory processing were tested in school aged children. The aim was to test whether the long-term changes in sensitivity reported in animal models, in regions both local to and distant from the injury site, could be observed in humans. To do this we used quantitative sensory testing (QST) in children aged 9–12 years who had undergone cardiac surgery in infancy. Cutaneous mechanical and thermal thresholds were measured at the thoracic scar region and at control contralateral thoracic and reference thenar areas in this early surgery group ($n = 9$), and compared with thresholds at the same regions in age and gender-matched controls ($n = 9$). The results showed that the cardiac surgery group was significantly less sensitive to von Frey hair tactile stimulation in the non-injured thenar area than the control group; mean threshold 5.02, SD ± 1.59 compared to 2.76, SD ± 0.79 (von Frey hair number, $p = 0.04$). In addition, their lateral thoracotomy scar areas were significantly less sensitive to von Frey hair stimulation (mean = 9.82, SD ± 1.97, $p < 0.001$) and to cooling and warming than any other site tested. Eight of the nine children in the early surgery group did not perceive warmth on their scars and were only able to detect uncomfortable heat as the temperature was raised. Three of these children felt a paradoxical cold prior to the hot sensation and all reported subtle abnormalities in everyday sensations. Questionnaires revealed perceived differences in pain perception, individual aberrant sensations and pain interfering with daily life that warrant further study. We conclude that tissue injured in early infancy remains measurably altered to mechanical and thermal stimulation in later life. These findings are consistent with the results of animal studies that early infant injury has not only local, but also global long-term consequences upon sensory processing.

Keywords: Paediatric pain; Childhood pain; Infant pain; Quantitative sensory testing; Mechanical thresholds; Thermal thresholds; Plasticity; Hyposensitivity; Paradoxical cold perception; Aberrant heat perception

1. Introduction

The postnatal period is a critical time in the development of sensory systems and it is increasingly evident that the developing nervous system is dependent upon postnatal neural activity, requiring defined patterns of afferent input for normal synaptic organisation to take place (Fitzgerald, 2005). Abnormal or excessive activity related to pain and injury in early life may therefore have the potential to cause long-term changes in somatosensory and pain processing (Anand, 2000; Fitzgerald and Walker, 2003). While a number of animal models have

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been established that show long-term changes in pain processing following infant inflammatory lesions (Al Chaer et al., 2000; Alvares et al., 2000; Anand et al., 1999; Bhutta et al., 2001; Ren et al., 2004; Reynolds and Fitzgerald, 1995; Ruda et al., 2000), the data in man are less clear. Follow-up studies of preterm infants who received care in neonatal intensive care units (NICU) show a number of interesting effects upon pain and sensory processing in childhood using psychological and behavioural assessments (Buskila et al., 2003; Grunau et al., 1994; Oberlander et al., 2000). More recently quantitative sensory testing revealed increased heat sensitization and depressed basal sensory thresholds in ex-NICU children (Hermann et al., 2006). While these reports are compelling, ex-NICU infants are a heterogeneous population and their assessment may be confounded by comorbidity, social and family factors (Grunau, 2002; Grunau et al., 2004). Follow-up studies of patients undergoing early surgery provide a different approach to the sensory effects of early injury on a potentially more homogeneous group. Circumcision at birth results in increased pain behaviour in response to inoculation at 4–6 months (Taddio et al., 1997) and surgery in the first 3 months of life is reported to lead to higher analgesic requirements upon subsequent surgery, 4 weeks to 2 years later, compared to previously unoperated children (Peters et al., 2005).

In this study we have used quantitative sensory testing (QST), which provides objective, reliable and repeatable measures of cutaneous sensation, to investigate the long-term consequences of early infant injury upon somatosensory processing. To do this we focussed upon a group of 9–12 year old children who had undergone major cardiac surgery in infancy compared to age and gender matched controls. The aim was firstly to measure cutaneous sensory thresholds in and around the thoracic surgical scar as a test of long-term localised effects of injury and secondly to measure cutaneous sensory thresholds in previously unaffected areas of the body to test global changes in sensory perception.

2. Methods

Children who had undergone neonatal cardiac surgery were recruited for this cross sectional comparative study because they had a relatively uniform injury, in terms of size and location to allow for group comparison, surgery was unilateral and not midline to allow for intra participant comparison, and the scar was visible, at an accessible site and a reasonable size for testing. At 9–12 years old, the participants were old enough to understand QST. The study protocol was approved by the Joint University College London/University College London Hospitals Committee on the Ethics of Human Research and by the Chairman of the Great Ormond Street Hospital for Children NHS Trust/Institute of Child Health Local Research Ethics Committee.

2.1. Recruitment

The children with lateral thoracotomy scars were recruited by searching through the operating notes from January 1991 to December 1993 of the Cardiothoracic Department at Great Ormond Street Hospital. We included infants who had their operation within the first month of life if born full term, or within 1 month corrected age if born preterm. The children's general practitioners (GP) were contacted to enquire about the appropriateness of contacting participants. Following their permission the medical notes were screened for the following exclusion criteria: hypoxic/ischaemic cerebral damage as diagnosed by ultrasound scan, neurological abnormalities on previous clinical examination, regular medication or drug use or chronic disease that could influence somatosensory function (e.g. diabetes mellitus), and a Wechsler Intelligence Scale for Children (Roth et al., 2001) score of <80, indicating cognitive impairment. Fifty suitable participants were identified and 72% of GPs responded. In some cases GP's did not recommend contact either due to complicated family situations ($n = 6$), or additional health problems ($n = 3$), resulting in 27 children receiving an invitation letter and information about the study. Ten families (37%) responded, one did not arrive for their testing appointment, therefore nine surgical children were tested. Control subjects were recruited through contacts of the researchers. At the testing appointment, verbal assent was obtained from the children and written consent was obtained from the parents. The children were made aware of their right to withdraw permission for the continuation of all or any portion of the tests.

2.2. Aetiology of the thoracic scar

The neonatal surgery group all had a lateral thoracotomy scar resulting from the repair of either a patent ductus arteriosus (PDA) or a coarctation of aorta (CoA) as neonates in the early 1990s. In both procedures, the thoracic skin was incised with a scalpel, and subsequent layers were opened using diathermy. Muscles were incised in layers, intercostal muscles and ribs were spread with artery forceps and the pleura entered. For closure, 3–4 heavy pericostal stitches were inserted, and the muscular layers, subcutaneous tissue and the skin closed. A drain was placed just caudal to the incision. Usual practice was for children to receive inhalation anaesthetic during the procedure and postoperative opioid analgesia during intensive care, followed by non-opioid analgesia as needed during the recovery period. On average, 10 years ago, patients with an uncomplicated repair of aortic coarctation spent 1 day in intensive care, 7 days on the high dependency unit, during which time the chest drain was removed, and a couple of days on a ward before discharge.

The demographics of the population are shown in Table 1. All the children were within 1 SD of height and weight norms for age, except one surgical participant who was between 1 and 2 SD of normal weight for height and age.

2.3. Study protocol

After familiarizing the participants with the situation and obtaining consent, the investigator took children through a detailed questionnaire designed to gain information about the location and sensations around any scars, their previous pain experience, frequency and intensity of nine common everyday pains, and current general health The questionnaire consisted of a body outline, numeric rating scale and forced choice items derived from previously validated pain assessment tools (Franck et al., 2000; Savedra et al., 1993; Turk and Melzack, 2001). Questions about the scar and area surrounding the scar probed issues of pain, discomfort, other sensations (numbness, tingling, itching, etc.) and the effects of clothing or other environmental conditions (e.g., cold, heat, tiredness, etc.). Questions about common pains probed frequency and intensity of headache, toothache, earache, sprains, bruises, backache, joint pain, abdominal pain, and menstrual pain. General health questions probed occurrence of injuries, hospitalisation, use of medication or other substances, acute and chronic health problems. A full copy of the questionnaire is available from the authors on request.

The participants were in seated position for testing the thenar eminence (reference area) and were lying on their sides for testing thoracic areas. They were asked to keep their eyes closed during testing and were not given auditory cues to indicate the start of a stimulus. All were given the same instructions to report verbally when they perceived a sensation of pressure, and to click the button to stop the test when they first perceived the sensation of coolness or warmth. Each participant was given a short demonstration before each type of test to familiarise them with the test. Participants with thoracic scars were tested on the reference area, the lateral thoracotomy scar site (left side of thorax) and the corresponding site on the contralateral side of the body as intra-subject control (right side of thorax). Each control participant was tested on the reference area and at the same thoracic sites as the surgery group. All participants were initially tested on the reference area. Half of the scar group was randomly allocated to be tested next on the scar site followed by the contralateral control site, and the other half of the group on the contralateral control site followed by the scar site. In the control group, half were randomly allocated to be tested first on the right site of the thorax and half first on the left. The testing procedure was well tolerated and no child withdrew from the protocol or reported discomfort or distress.

We chose the thenar eminence as the reference area as this has been used in previous studies and reference intervals for thermal testing are available (Hilz et al., 1996; Hilz et al., 1998 b,a; Meier et al., 2001; Zohsel et al., 2006). Only one child had had a radial arterial line, three had brachial, two posterior tibial and one child a line in the umbilical artery. In two cases there was no information available.

Table 1
Birth and surgery history

	Neonatal cardiac surgery group	Control group
Participants	$N=9$	$N=9$
Age (years) at testing (mean ± SD)	10.56 ± 0.88	10.56 ± 0.88
Gender	4 Girls, 5 boys	4 Girls, 5 boys
Ethnicity	8 Caucasian 1 Afro-Caribbean	7 Caucasian 2 Afro-Caribbean /Caucasian
Preterm	$N=3$ (26*, 30**, 35*** weeks)	$N=0$
Fullterm	$N=6$	$N=9$
Cardiac surgery	CoA, $N=5$; PDA, $N=4$	N/A
Age at surgery	3–9 weeks (preterm group), 1–4 weeks (term group)	
Scars	Lateral thoracotomy scars in the 3rd–5th intercostal region; length 12–24 cm; width 2–5 mm	
Additional surgery	Preterm: $N=3$ *hernia repair 7 months of age (5S) **bowel surgery for necrotising enterocolitis at 6 days (6S) *** Minor surgery in childhood: grommets, circumcision (9S) Fullterm: $N=3$ #ventricular septal repair at 1 year (4S) #atrial septal defect repair at 13 months (8S) #subaortic stenosis repair at 9 years (3S)	$N=1$, strabismus surgery at 4 years

2.4. Quantitative sensory testing

Mechanical perception threshold, cool and warm perception thresholds and brush allodynia were tested on each site. Mechanical perception threshold was tested using hand-held von Frey hairs (Bell-Krotoski et al., 1995), a series of 20 nylon filaments arranged in a logarithmic series of increasing force as shown in Table 2. Thermal thresholds were measured using a handheld Sense lab MSA Thermal Stimulator (Somedic, Sweden) with an 18 mm × 18 mm (3.24 cm^2) contact thermode. Brush allodynia was tested by stroking the skin with a Sense lab brush with an applied force of 200–300 mN.

2.4.1. Mechanical perception threshold

The following algorithm was repeated five times at control sites and at scar sites, both on the scar and at a distance of 3–5 mm from the scar: (i) *appearance threshold*: Von Frey hairs were applied sequentially at gradually increasing forces until the participant felt touch (ii) *disappearance threshold*: Von Frey hairs were applied at decreasing intensities starting with the hair noted as "appearance threshold" until no touch was felt. The filaments were applied perpendicular to the skin for one second until they buckled, maintained in place for one second and then removed. The site of stimulation was very slightly altered each time to avoid habituation. The actual threshold was determined as the mean of all ten values.

2.4.2. Thermal threshold

The thermode baseline temperature was maintained at 32 °C and the cut-off temperature limits were 10 °C and 50 °C. To test thermal thresholds the temperature was decreased or increased by 1 °C per second and the participant was asked to press a button when cool or warm sensations were first felt. This returned the thermode temperature to baseline temperature at a rate of 2 °C per second. This procedure was repeated 10 times. The mean value of the 10 sets of stimuli was taken as the threshold.

Table 2
Von Frey hair number and stimulus intensity

Hair number (vFh unit)	Grams (g)	milliNewtons (mN)	% Increase
1	0.0174	0.1706	66
2	0.0292	0.2863	66
3	0.0479	0.4697	66
4	0.0794	0.7785	66
5	0.132	1.2943	66
6	0.219	2.1475	66
7	0.363	3.5595	66
8	0.603	5.9130	66
9	1.00	9.80	66
10	1.66	16.27	66
11	2.75	26.95	66
12	4.57	44.79	66
13	7.58	74.28	66
14	12.6	123.48	66
15	20.9	204.8	66
16	34.7	340.1	66
17	57.5	563.5	66
18	95.5	935.9	66
19	159.0	1558.2	66
20	263.0	2577.4	66

2.4.3. Brush allodynia

Brush allodynia was tested by applying strokes with a force of 200–300 mN. Each site was stroked 3 times with the brush, at 3-s intervals. The participants were asked to score the sensation with a number between 0 and 100, with 0 being neutral/comfortable and 100 being most unpleasant/painful. The mean of three brush scores was calculated.

2.5. Statistical analysis

Statistical analysis was conducted using Minitab software Release 13 for Windows (Minitab Inc., Pennsylvania, PA, USA). All mechanical perception threshold data were analysed using von Frey hair number units (vFh units; see Table 2), which correspond to a logarithmic transformation (Cole, 2000).

Analyses of the effects of site (reference, left and right thoracic), group (scar or control), and individual participant effect, on thresholds for all modalities (von Frey perception, cool and warm perception), were performed using nested univariate analysis of variance (ANOVA), after first checking assumptions of normality. The interaction between site and group was also examined. Post hoc comparisons of all pairwise combinations within and between groups were made using the Tukey method.

For the questionnaire data, the differences between surgery and control groups in the numbers of pains experienced and the amount of worst pain from these pains were compared using the Mann–Whitney test for unpaired observations. For all statistical tests, $p \leqslant 0.05$ was considered statistically significant.

3. Results

3.1. Initial analysis

Initial analyses (nested ANOVAs) revealed that, for von Frey perception and cool perception in all participants, there was a significant effect of group (von Frey, $p < 0.001$; cool, $p = 0.015$), and site (von Frey, $p < 0.001$, cool $p = 0.015$) on threshold. Furthermore, an interaction was noted between group and site (von Frey, $p = 0.015$; cool, $p = 0.048$). A similar pattern was found for warm perception, the only difference between this and the other two modalities being the lack of a group effect, although the effect of site was significant ($p < 0.001$), as was the interaction between group and site ($p = 0.002$). For all modalities, there was no individual subject effect across the two groups (von Frey perception, $p = 0.283$; cool perception, $p = 0.09$; warm perception, $p = 0.072$). Following the initial ANOVA, Tukey's post hoc comparisons revealed the following results.

3.2. Mechanical (von Frey hair) perception

Fig. 1 shows two important effects. Firstly, surgical participants had significantly decreased sensitivity to von Frey hair mechanical stimulation at the thoracic scar site (9.82 ± 1.97; mean ± SD) compared to the contralateral, unaffected thoracic site (6.82 ± 1.88), and compared to the reference area (5.02 ± 1.59). The thoracic scar site also was less sensitive than the left and right thoracic sites of the control participants (6.55 ± 1.37 and 6.67 ± 1.37 respectively). In control participants, perception of mechanical stimuli at the left thoracic and right thoracic sites did not differ from each other or from the unaffected right thoracic site in the surgical group.

The second major finding was that the surgical group was significantly less sensitive to touch at the thenar eminence (reference site) than the control group. As expected, the threshold of the control group reference area was significantly more sensitive compared to any other area tested (see Fig. 1).

3.3. Cool perception

Fig. 2 shows that the surgery group also had a significantly decreased cool sensitivity over the thoracic scar site (25.05 ± 6.28 °C) compared to the contralateral unaffected thoracic site (29.44 ± 0.82 °C), and the reference area (29.26 ± 1.84 °C). The thoracic scar site also was less sensitive than the left and right thoracic site in the control group (29.49 ± 2.20 °C and 29.84 ± 1.12 °C, respectively). Again, sensitivity of the left thoracic and right thoracic sites of the control participants did not differ from each other or from the unaffected right thoracic site in the scar group.

There was no significant difference in cool threshold in the reference areas of the surgical and control groups. There was also no difference of either reference area to the contralateral control site in the scar group, or to both thoracic sites in the control group.

3.4. Warm perception

Testing this modality revealed the same pattern as with cool perception. Fig. 3 shows that the surgery group had a significantly decreased warm sensitivity at the thoracic scar site (41.46 ± 3.71 °C) compared to the contralateral unaffected thoracic site (37.08 ± 2.00 °C) and the reference area (34.84 °C ± 0.87 °C). The thoracic scar site was also less sensitive than the left

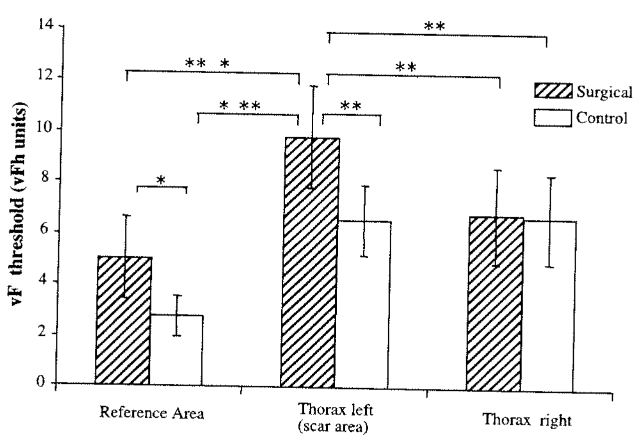

Fig. 1. Von Frey perception thresholds. In the surgical group, the mechanical threshold at the neonatal scar site was significantly higher than the contralateral unaffected side ($p = 0.0032$), and the reference area ($p = 0.0000$). The scar site also was less sensitive than the left thoracic ($p = 0.0012$) and right thoracic site of the control group ($p = 0.0019$). In control participants, perception of mechanical stimuli at the left thoracic and right thoracic sites did not differ from each other or from the right thoracic, unaffected site of the surgical group. The surgical group were also significantly less sensitive to touch at the thenar eminence (reference site) than the control group ($p = 0.043$). The threshold of the control group reference area was significantly more sensitive than any other area tested ($p \leqslant 0.0002$) $N = 9$ per group, error bars ± SD.

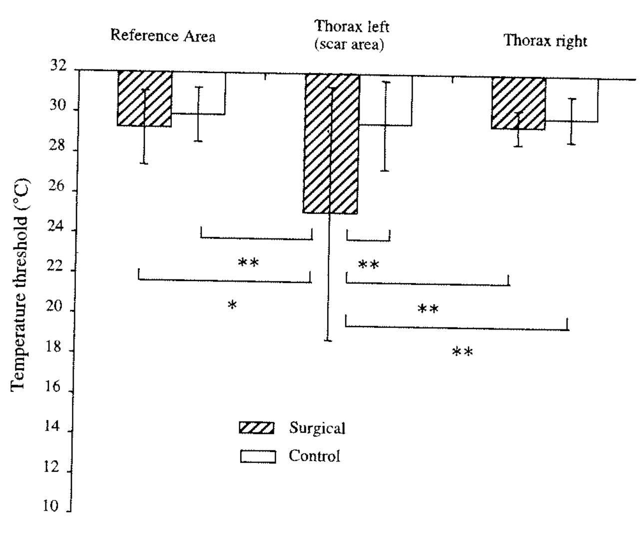

Fig. 2. Cooling thresholds at the injury site; comparisons in sensitivity to cool stimulation between scar and contralateral thoracic areas. The surgical group had a significantly increased cool perception threshold at the neonatal scar site compared to the contralateral unaffected site ($p = 0.0140$) and the reference area ($p = 0.0203$). The scar site also was less sensitive than the left thoracic and the right thoracic site in the control group ($p = 0.0127$ and $p = 0.0061$ respectively). The sensitivity of the left thoracic and right thoracic sites of the control participants did not differ from each other or from the right thoracic unaffected site in the scar group. $N = 9$ per group, error bars ± SD.

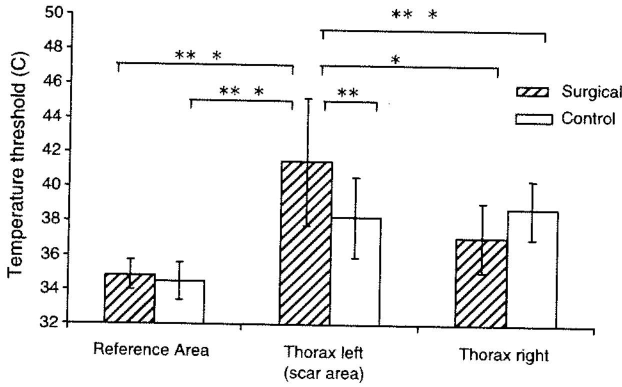

Fig. 3. Warm thresholds at the injury site; comparisons in sensitivity to warm stimulation between scar and contralateral thoracic areas. The surgical group had a significantly increased warm perception threshold over the neonatal scar site compared to the contralateral unaffected thoracic site ($p = 0.0004$) and the reference area ($p = 0.0000$). The scar site was also less sensitive than the left thoracic ($p = 0.0127$) and the right thoracic site ($p = 0.0061$) in the control group. Warm sensitivity of the left thoracic and right thoracic sites of the control participants did not differ from each other ($p = 0.9942$) or from the unaffected right thoracic site in the scar group ($p = 0.8033$ and 0.4818 respectively). Both reference areas were significantly more sensitive to warming than the left and right thoracic sites of the control group ($p < 0.0087$) but not the right thoracic site of the scar group. $N = 9$ per group, error bars ± SD.

and right thoracic site in the control group (38.71 ± 1.72 °C and 39.22 ± 2.35 °C, respectively). Again sensitivity of the left thoracic and right thoracic sites of the control participants did not differ from each other or from the right, unaffected thoracic site of participants in the surgery group.

There was no significant difference between the warm threshold in the reference areas of the surgical and control groups. Both reference areas were significantly more sensitive to warming than the left and right thoracic sites of the control group ($p = 0.009$) but not the right thoracic site of the surgery group.

3.5. Abnormal thermal sensation at the injury site

Not only were thermal thresholds increased at the thoracic scar site but there was a striking difference in the pattern of thermal perception on the scar site compared to the contralateral unaffected thoracic site in the surgery group. In eight out of nine participants, children spontaneously reported a 'hot' sensation on establishing the thermal threshold (41.46 °C ± 3.71) for the scar site. This was not anticipated or described in a questionnaire; all eight children simply said 'it feels hot' and failed to report a warm sensation. None of them said it was 'sore' or 'painful'. In addition, three of the participants reported a brief feeling of cool before the hot sensation. The child who did not report this "hot" sensation was obese. This pattern of abnormal thermal sensation is depicted in a diagram in Fig. 4.

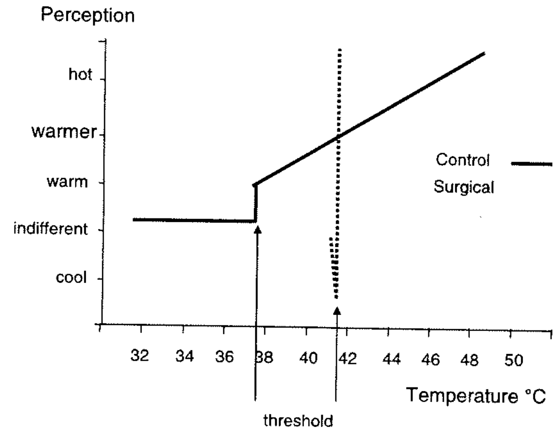

Fig. 4. A diagram depicting the pattern of warmth and heat detection in the surgical and control group.

3.6. Brush allodynia

Two of the children in the neonatal thoracic surgical group felt slightly uncomfortable when stroked with the brush over the scar (mean rating: 2.63 ± 6.63,SD) and the same children reported slight discomfort over the contralateral thoracic (mean rating: 4.11 ± 10.48) and thenar eminence sites (1.93 ± 4.11). None of the children from the control group reported any discomfort.

3.7. Altered pain and sensations in daily life

The average rating for the nine common pains was higher for the neonatal surgery group than the control group (6.87 ± 2.69 vs 4.07 ± 2.62), but this was not statistically significant ($p = 0.071$). Two of the children in the control group thought that they experienced more pain than their friends, whereas three children in the surgery group felt they experienced less pain than their friends. More children in the surgery group reported specific pains, and three children also reported aberrant sensations in daily life (Table 3). For example, one participant reported that her scar felt slightly thicker than the surrounding area and less ticklish and her clothes, especially a bikini or crop top could feel a little uncomfortable. She noted the same phenomenon with warm and hot water. Two of these children had common pains that interfered with their lives (migraine, leg cramps). The same two children had also high ratings concerning their most painful experience ever.

4. Discussion

The aim of this study was to investigate the long-term consequences of neonatal injury upon somatosensory processing. The results demonstrate specific sensory differences in previously injured and uninjured areas of the

Table 3
Aberrant sensations on thoracic scar site and reported in daily life

Neonatal surgery participant	Cool perception threshold mean ± SD (min temp)	Warm perception threshold mean ± SD (max temp)	Brush discomfort mean ± SD (site)	Notable pain and sensations in daily life	Control participant	Cool perception threshold mean ± SD (min temp)	Warm perception threshold mean ± SD (max temp)	Brush discomfort mean ± SD (site)	Notable pain and sensations in daily life
1S	23.3 ± 2.3 (19.9)	46.8 ± 2.5 (49.5) • Felt no warm, only hot	0		1C	29.1 ± 0.3 (28.6)	37.7 ± 4.4 (45.5)	0	
2S	23.6 ± 1.6 (21.6)	40.28 ± 0.8 (41.0)	0		2C	30.7 ± 0.3 (30.3)	38.6 ± .4 (38.8)		
3S	23.7 ± 1.4 (21.9)	45.5 ± 1.3 (46.8) • Felt no warm, only hot • Felt cool before hot	0	• Felt less pain than friends • Higher worst pain ratings than present cohort • Migraine pain interferes with daily life	3C	30.62 ± 0.5 (29.7)	37.1 ± 0.7 (38.3)	0	• Felt more pain than friends • Knee pain interferes with daily life
4S	16.7 ± 5.7 (10.0)	36.7 ± 3.4 (40.7) • Felt no warm, only hot	0		4C	29.06 ± 0.6 (28.3)	44.2 ± 1.1 (45.4)	0	
5S	28.5 ± 0.84 (27.1)	38.5 ± 2.8 (41.4) • Felt no warm, only hot • Felt cool before hot	0		5C	30.5 ± 0.8 (29.9)	36.6 ± 2.8 (39.8)	0	• Felt more pain than friends
6S	10.6 ± 1.3 (10.0)	44.0 ± 4.0 (48.4) • Felt no warm, only hot	3.7 ± 3.1 (thoracic scar) 5.3 ± 4.5 (contralateral thoracic site) 5.67 ± 4.93 (thenar eminence)	• Felt less pain than friends • Higher worst pain ratings than present cohort • Unpleasant scar sensations with clothing touching	6C	30.2 ± .4 (29.5)	40.0 ± 0.4 (39.4)	0	
7S	29.6 ± 0.3 (29.3)	38.3 ± 4.6 (43.6) • Felt no warm, only hot	20 ± 10 (thoracic scar) 31.7 ± 2.9 (contralateral thoracic site) 11.7 ± 2.9 (thenar eminence)	• Felt less pain than friends • Higher worst pain ratings than present cohort • Migraine, leg cramps interfere with daily life • Unpleasant scar sensations with clothing touching	7C	23.9 ± 3.5 (19.6)	37.4 ± 0.6 (38.5)	0	• Occasional chest pain interferes with daily life
8S	29.9 ± 0.7 (29.0)	38.7 ± 2.2 (40.2) • felt no warm, only hot	0	• Knee pain interferes with daily life	8C	30.2 ± 0.6 (29.3)	37.3 ± 2.2 (39.4)	0	
9S	28.6 ± 0.68 (27.9)	44.3 ± 5.9 (50.0) • felt no warm, only hot • felt cool before hot	0	• Occasional thoracic pain with stretching	9C	30.8 ± .4 (30.3)	38.4 ± .50 (38.9)	0	

The number in the parentheses represents the minimum or maximum temperature or site of brush discomfort for each subject. Values are mean and standard deviation.

body in children who have undergone surgery as neonates, when compared to controls. The neonatal scar area was significantly less sensitive to touch, cool and warm stimulation than all other sites tested suggesting that sensory thresholds remain generally higher in the damaged area. Warm hyposensitivity was linked to aberrant heat perception because an immediate sense of hot was perceived at 41 °C or above, with no preceding sense of warmth. Furthermore three of the participants had a brief paradoxical cool sensation before the feeling of heat. A further notable difference was that the thenar eminence was significantly less sensitive to mechanical stimulation in the neonatal thoracic surgery group compared to the control group, suggesting that these children remain globally hyposensitive to touch.

4.1. QST in children

QST has been widely used in adults to examine various medical conditions involving peripheral neuropathies, CNS pathology or trauma in the adult (Zaslansky and Yarnitsky, 1998) and reference values are available for von Frey filaments, vibration and thermal testing (Bell-Krotoski et al., 1995; Yarnitsky and Sprecher, 1994). QST in children has been used much less widely. However, the reference site cool and warm thresholds in the present study are within the published range of thermal detection thresholds in normal children (Hilz et al., 1996; Hilz et al., 1998 b,a; Meier et al., 2001). The reference area thresholds of our control group are also consistent with the normal values for touch perception in children examined with Semmes–Weinstein monofilaments at the same segmental level (Thibault et al., 1994); thresholds in our surgical group are higher, supporting our conclusion that these children have a baseline hyposensitivity to touch.

An important consideration is the presence of parents during testing (Chambers et al., 2002; Tsao et al., 2006). Anxiety, fatigue, attention and cooperation are important factors in children's sensory perception and thresholds can be affected by maternal presence (Zohsel et al., 2006), but this was not examined here.

4.2. Strengths and weaknesses

The study is the first time that quantitative methods have been used to assess long-term somatosensory changes in previously injured and intact skin, a decade after neonatal surgery. The large, visible thoracic scar facilitated testing and provided comparative control data from the contralateral area of the body in each participant for comparison. A major limitation, however, is the restricted sample size making this a preliminary study. The numbers are small and yet the group is relatively homogeneous and the variability between participants is statistically non-significant. The effort involved for both parents and children to come to be tested meant that all the participants were highly motivated, a very important factor for QST (Siao and Cros, 2003). Nevertheless factors beyond our control such as too little sleep the night before testing,cannot be ruled out and nor can the possibility of sampling bias, perhaps because of differing motivation or increased family sensitivity of the consenting participants. Detailed information about the length of hospital stay, anaesthetic and pain management and exact surgical protocols were not available for our sample and this is also an important consideration. Interpretation of the effects of early surgery on average daily pains must be interpreted with caution due to the small sample size and indeterminate p value.

No directly comparable studies have been performed in adults but somatosensory changes have been reported 18 months after adult burns. Thresholds, particularly to touch and cold, are significantly higher in burned patients than in control participants both at the site of injury and at contralateral uninjured sites although a reference site at a different segmental level has not been tested (Malenfant et al., 1998).

In a study of tender points in 60 adolescents (12–18 years), prematurely born children were found to have significantly more tender points and generally lower tenderness thresholds but did not report any increased pain or stiffness in their daily life (Buskila et al., 2003). The present study examined cutaneous thresholds to touch and temperature, rather than deep connective tissue responses to pressure pain and therefore the two studies are hard to compare.

4.3. Mechanisms underlying decreased sensitivity at the scar

The decreased sensitivity at the scar site was clear when compared to both the contralateral site on the same segmental level in the thoracic scar group, as well as the control group, suggesting changes in sensory terminals at the actual site of wounding or in the somatosensory circuitry involving specifically the injured side at its segmental level. Damage to all sensory afferent nerve fibres in the scarred tissue as a result of the deep tissue surgical injury could cause long-term hyposensitivity over the injured area, but if so, the damage must have spread outside the scar itself as von Frey testing was 3–5 mm from the scar. Adult scar tissue does have fewer nerve fasciculi compared to normal skin (Zhang and Laato, 2001) but neonatal or childhood scar tissue has not been examined in this way. Nerve damage in young rats can lead to sensory neuron cell death in the dorsal root ganglion, reduced soma-dendritic growth of spinal sensory neurons and changes in descending projections (Fitzgerald and Shortland, 1988; Shortland and Fitzgerald, 1991; Shortland and Fitzgerald, 1994).

More superficial skin wounds appear to have the opposite effect, resulting in hyper – rather than hyposensitivity (Hermanson et al., 1987). In animal models superficial skin wounding triggers a prolonged local sprouting response in the sensory nerve terminals in the injured area which decreases progressively with age at wounding and is accompanied by a long lasting hypersensitivity and lowered mechanical thresholds in the injured area (Moss et al., 2005; Reynolds and Fitzgerald, 1995). The increased production of neurotrophins and decreased levels of inhibitory factors in damaged skin appears to encourage hyperinnervation of inflamed skin (Moss et al., 2005) but if the deafferentation is sufficiently great, this may not be possible.

4.4. Aberrant heat sensations

Deafferentation at the scar site could also play a role in the immediate heat sensation reported by the surgical group when warming the scar region, preceded in some cases by a momentary feeling of cold. Warm sensation is mainly conveyed by specific warm receptors with unmyelinated C fibres that are optimally excited in the innocuous temperature range (Hallin et al., 1982). In general, heat pain arises from excitation of C-polymodal nociceptors which evoke a 'burning' sensation, with some contribution from Aδ nociceptors which evoke a 'sharp prickling' quality (Verdugo and Ochoa, 1992). In adult small fibre neuropathies, the loss of C unmyelinated fibres blunts warm sensation, while sparing thermal pains. Unlike C mediated warm sensation, C mediated thermal pains have little requirement for spatial summation so that the threshold function remains normal for thermal pains despite a marked reduction in afferent fibres (Verdugo and Ochoa, 1992). A possible depopulation or destruction of C fibres in the scar tissue could therefore explain our observation.

Our protocol was intended to detect 'warm' rather than 'hot' thresholds but at the scar site only a 'hot' sensation was detected at 41.46 °C ± 3.71 °C which is in the normal range for heat pain thresholds this age in other regions (Zohsel et al., 2006). This suggests that there is no change in the detection of 'hot' per se, but a lack of preceding warm sensations which can act as an alerting or warning signal. However, the report of paradoxical cooling before the sense of heat is reminiscent of aberrant neuropathic sensations in adults (Rolke et al., 2006) and is consistent with the suggestion that integrity of non-noxious thermal systems is essential for the normal perception of thermal pain, and that the subjective sensation of pain depends on the integration of information from nociceptive and non-nociceptive channels (Defrin et al., 2006).

4.5. Mechanisms underlying baseline hyposensitivity

The hyposensitivity observed in the reference area suggests that central changes have also occurred that affect sensory processing and was also reported in ex-NICU patients of the same age (Hermann et al., 2006). This is consistent with animal studies showing generalized, long-lasting hypoalgesia following early injury (Ren et al., 2004; Wang et al., 2004). Rat pups subjected to low dose hindpaw inflammation at birth not only have a localised enhancement of hyperalgesia on re-inflamation of the affected paw but also a generalised reduction of baseline mechanical and thermal sensitivity all over the body which is not apparent until the animal is over 4 weeks old (Ren et al., 2004). Alterations in the hypothalamic-pituitary-adrenocortical axis (Charmandari et al., 2005) or the corticolimbo-brainstem descending pain/stress modulatory circuitry (Fields, 2000) could be triggered by early stress in the neonatal surgery group. In animal models neonatal stress is most often mimicked by handling and maternal separation (Sternberg and Ridgway, 2003). The mother's tactile contact with the pups influences their future reaction to stress (Winberg, 1998); more "tactile" mothers' offspring show a lower corticosteroid release during stress. These observations may be highly relevant to our neonatal surgical group, but remain speculative.

It is notable that the decreased baseline sensitivity observed here was restricted to touch perception and not observed for cool and warm perception. While the underlying central changes may be modality specific it is also possible that our subjects were better able to detect small changes in touch than in temperature. Furthermore, spatial and temporal discrimination may be a factor; in these studies touch thresholds were measured with von Frey hairs of 0.08 mm–1 mm in logarithmic steps of increasing force, whereas thermal perception was tested using a thermode of 18 × 18 mm with temperature increasing at 1 °C/s. The lower sensitivity and receptor density of the thoracic region (Weinstein, 1968) may explain the absence of hyposensitivity in the contralateral thoracic site.

4.6. Impact

The sensory changes found whilst testing appeared to have subtle impact on the day to day life of some of the children and these findings warrant further detailed prospective investigation of perceived pain, functional interference and pain coping using validated measures (Franck et al., 2002; Reid et al., 1998; Varni et al., 1987). Other variables such as temperamental style and family function should also be explored (Franck et al., 2004).

It seems likely that long-term alterations in sensory and pain processing following tissue or nerve insult during infancy reflect underlying plasticity in the peripheral and central sensory pathways (Fitzgerald, 2005). This preliminary study indicates that there are indeed consequences of early surgery in infants that have both local and global effects upon somatosensory perception in school aged children. Further research is needed to detect whether this has any impact upon pain experiences and reactions in the future.

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