The emergence of hierarchical somatosensory processing in late prematurity

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Abstract (max 200 words)

The somatosensory system has a hierarchical organization. Information processing increases in complexity from the contralateral primary sensory cortex to bilateral association cortices and this is represented by a sequence of somatosensory event related potentials of increasing latencies, recorded in scalp EEGs. The mammalian somatosensory system is known to mature over the early postnatal period in a rostro-caudal progression, but little is known about the development of hierarchical information processing in the human infant brain. To investigate the normal human development of the somatosensory hierarchy, we recorded event related potentials evoked by mechanical stimulation of hands and feet in 34 infants between 34 and 42 weeks corrected age, with median postnatal age of 3 days. We show that the shortest latency potential was evoked from both hands and feet at all ages with a stable contralateral somatotopic distribution. However, the longer latency responses matured with age, gradually emerging for the foot and, although always present, showing a shift from contralateral to bilateral hemispheric activation for the hand. These results demonstrate the rostro-caudal development of human somatosensory hierarchy and suggest that development of the higher tiers of this hierarchy are complete only just before normal birth, when bilateral integration becomes possible.

Keywords (max 5)

EEG; Preterm neonates; Brain development; ERP; mechanical stimulation
The processing of somatosensory information in the mammalian cortex has a hierarchical organization. Features of increasing complexity are encoded in an ascending system of connected cortical areas and functions to allow, for example, the localization and then conscious perception of the various qualities of touch (Felleman and Essen 1991; Yoshiaki Iwamura 1998; Dijkerman and Haan 2007). Areas within primary somatosensory cortex (SI) sequentially encode the location and characteristics of contralateral somatosensory input on the body, before the secondary somatosensory cortex (SII) integrates information from the two body sides and projects on to association areas which integrate multiple sensory modalities, facilitating object recognition and motor planning (Kandel, Schwartz, and Jessell 2000). Early somatosensation may contribute to survival behaviours such as feeding, rudimentary motor skills like grasping, and to the beneficial effects which parenting provides (Hackman, Farah, and Meaney 2010; Molina et al. 2015).

In rodents, the somatosensory architecture develops over the first few postnatal weeks, which correspond to the last trimester of gestation in humans (Colonnese et al. 2008) and follow a rostro-caudal developmental gradient. This is clear from the sequential organization of SI: (i) neurons in SI initially respond almost exclusively to whiskers stimulation, while responses to forelimb appear later finally followed by responses to hindlimb stimulation (McCandlish, Li, and Waters 1993; Seelke, Dooley, and Krubitzer 2012); (ii) amputation of the forelimb at P0 results in the corresponding SI representation to respond to hindlimb, but not whiskers stimulation suggesting that inputs from the facial area have already matured at birth (Pluto et al. 2003). In addition, complex sensory-motor interactions such as placing (i.e. lifting a paw and placing the sole flat on a support platform) in response to a gentle touch of the dorsum develops for the forelimb before the hindlimb (Donatelle 1977). In line with these findings in animal models, upper limb grasp is more common than lower limb grasp in full-term neonates (Colson, Meek, and Hawdon 2008). However, little is known about when the different levels of the somatosensory processing pathway mature in humans, or whether this maturation occurs first for the upper limbs.
The connections which allow the flow of the tactile information along the somatosensory processing pathway structurally develop and refine across the third trimester and perinatal period. Cortical layer IV begins to differentiate between 20-26 weeks of gestation (Burkhalter, Bernardo, and Charles 1993; Rees, Walker, and Jennings 2010) with early thalamo-cortical contacts, synaptogenesis and vertical inter-layer connections occurring from 24-26 weeks (Flower 1985; Burkhalter, Bernardo, and Charles 1993; Volpe 2009). However, synaptogenesis of thalamo-cortical and cortico-cortical connections is most pronounced from 28 weeks until full-term age, in line with extensive dendritic development (Flower 1985). The entry of callosal fibres into the cortex from 33 weeks (Volpe 2009), disappearance of the somatosensory subplate from 36 weeks (Kostovic and Rakic 1990), dense intra-layer horizontal cortical connections by 37 weeks (Burkhalter et al. 1993), and a peak in axon growth within the parietal white matter at 38-42 weeks (Haynes et al. 2005) suggests that the inter- and intra-hemispheric cortico-cortical circuits necessary for higher-order somatosensory functioning may mature within the late pre-term and perinatal period.

Somatosensory processing can be investigated by recording scalp electroencephalography (EEG) and analysing the multiple somatosensory evoked potentials (SEPs) arising in response to stimulation. Indeed, in adults, scalp-recorded SEPs have been linked to different levels of the processing hierarchy of tactile information: early SEPs, consistent with a source in SI (Truett Allison, McCarthy, and Wood 1992), are recorded in adults even if stimuli do not elicit conscious perception, whereas later SEPs from 80 to 500 ms, likely to be generated beyond SI, such as in SII (Frot and Mauguière 1999; Hoechstetter et al. 2001), are only recorded if the stimulus has entered awareness (Libet et al. 1967; Kitazawa 2002).

The maturation of higher-level somatosensory processing in the developing preterm brain is poorly understood because the majority of studies have focussed only on the primary afferent volley. At 29-
33 weeks just a rudimentary response can be elicited by somatosensory stimulation (Milh et al. 2007; Whitehead, Pressler, and Fabrizi 2016) while by full-term age the somatosensory response comprises a sequence of positive and negative SEPs, as in adults (Karniski et al. 1992; Fabrizi et al. 2011). The first of these events in response to hand stimulation is a negative-positive complex (N1-P1) (Desmedt and Manil 1970; Hrbek, Karlberg, and Olsson 1973; Laget et al. 1976; Karniski et al. 1992; Taylor, Boor, and Ekert 1996) over the contralateral central area occurring between 30-100 ms, or a positive deflection (P1, 37-50 ms) over the midline central area following stimulation of the foot (Vaughan 1975; Georgesco et al. 1982; Gilmore et al. 1987; White and Cooke 1989; Minami et al. 1996; Pike, Marlow, and Dawson 1997). The somatotopic organisation of the electric and magnetic field of these early potentials is that of a forward pointing dipole consistent with activity in Brodmann Area (BA) 3b of the primary somatosensory cortex (SI) representation of the stimulated limb indicating the arrival of the peripheral afferent volley (Pihko et al. 2004; Lauronen et al. 2006; Minami et al. 1996; Pike, Marlow, and Dawson 1997).

Much less is known about longer-latency responses, which are considered to reflect higher-order processing levels further along the hierarchical tree (Nevalainen, Lauronen, and Pihko 2014; Saby, Meltzoff, and Marshall 2016). Following the early N1 and/or P1, stimulation of the hands and feet elicits a second negative deflection (N2) at 150 ms and, less consistently reported, a second positive peak (P2) at about 240 ms and a third negative peak (N3) at 450 ms (hands: Desmedt and Manil 1970; Hrbek, Karlberg, and Olsson 1973; Laget et al. 1976; Karniski et al. 1992; Taylor, Boor, and Ekert 1996; Pihko et al. 2004; Nevalainen et al. 2015; feet: Cindro, Prevec, and Beric 1985; Minami et al. 1996; Pike, Marlow, and Dawson 1997; Cindro, Prevec, and Beric 1985; Slater et al. 2010; Fabrizi et al. 2011). These later potentials are often prominent at the midline (Desmedt and Manil 1970; Hrbek, Karlberg, and Olsson 1973; Karniski et al. 1992; Karniski 1992) and, while N2 and N3 does not have a clear magnetic counterpart or origin, the symmetric electric and magnetic fields of P2 clearly represent a bilateral activation of the secondary somatosensory cortex (SII) in the parietal operculum (Pihko et al. 2004; Nevalainen et al. 2015; feet: Cindro, Prevec, and Beric 1985; Minami et al. 1996; Pike, Marlow, and Dawson 1997; Cindro, Prevec, and Beric 1985; Slater et al. 2010; Fabrizi et al. 2011).
2004, Nevalainen et al. 2008, Nevalainen et al. 2015). This indicates that a hierarchical organization is already present in term infants, however when this emerges in development is not known.

We hypothesised that the intra- and inter-hemispheric cortical changes that may underpin somatosensory processing could be functionally reflected in the emergence of specific SEPs and changes in their topographical distribution in humans. To address this, we recorded SEPs following tactile stimulation of all four limbs in late pre-term and full-term neonates with a corrected gestational age (CGA) of 34-42 weeks, where corrected gestational age is defined as gestational age (GA) at birth + postnatal age. To ensure that our data reflect intrinsic somatosensory maturation, and are not affected by experience, our cohort has a median postnatal age of just three days.

Materials and Methods

Subjects

Thirty-four infants evenly spread between 34+5 – 42+5 CGA (weeks + days) were recruited for this study from the postnatal ward and special care baby unit at the Elizabeth Garrett Anderson wing of University College London Hospitals between September 2015 and July 2016 (Table 1). No neonates were acutely unwell, receiving neuroactive medication or receiving respiratory support at the time of study. Infants were neurologically normal both at the time of study and at the date of discharge based on review of medical notes and the discharge summary. No subjects had congenital abnormalities except for a single neonate with a cleft lip. Cranial ultrasound scans were reported as normal when subjects were referred for one (n = 6, including the baby with a cleft lip). All EEGs were assessed as normal for CGA by a clinical neurophysiologist (KW) according to Tsuchida et al. 2013: developmental features included alternating patterns and frequent delta brushes in the youngest infants and
continuous multi-frequency activity, with no delta brushes, in the oldest infants (supplementary Fig. 1).

Ethical approval was obtained from the University College Hospital ethics committee, and informed written parental consent was obtained prior to each study. The study conformed to the standards set by the Declaration of Helsinki guidelines and was well tolerated: 28/30 of the neonates who were asleep at study onset slept through the whole protocol.

Vigilance state prior to stimulation of each limb was categorised according to EEG and respiratory criteria as wakefulness or active sleep in 72/113 and quiet sleep in 41/113 with no significant difference according to CGA (binary logistic regression p = .124), or which of the four limbs was stimulated (Pearson Chi-Square p = .433).

**EEG recording**

Recording electrodes (disposable Ag/AgCl cup electrodes) were positioned according to the modified international 10/10 electrode placement system, with high density central-parietal and temporal coverage, at F7, F8, F3, F4, Cz, CPz, C3, C4, CP3, CP4, T7, T8, P7, P8, TP9, TP10, O1 and O2. Occasionally FCz was also used. A reduced number of electrodes were applied if the infant became unsettled during set-up. The reference electrode was placed at Fz (Pike, Marlow, and Dawson 1997; Tombini et al. 2009; Vanhatalo et al. 2009; Trollmann, Nüsken, and Wenzel 2010) and the ground electrode was placed at FC1/2. Target impedance of electrodes was <10 kΩ (André et al. 2010). A single lead I ECG was recorded from both shoulders. Respiratory movement for sleep staging was monitored with an abdominal movement transducer. EEG was recorded with a direct current (DC)-coupled amplifier from DC-800Hz using the Neuroscan (Scan 4.3) SynAmps2 EEG/EP recording system. Signals were digitized with a sampling rate of 2 kHz and a resolution of 24 bit.
Tactile stimulation

Mechanical taps were delivered by KW to the lateral edge of the infants’ palms and heels using a hand-held tendon hammer with a 15mm² contact surface (supplementary Video 1). The hammer had a piezo-electric transducer that allowed to measure the force applied at each tap, and to record the precise timing of the stimulation on the EEG recording (Worley et al. 2012). A train of maximum 48 somatosensory stimuli was delivered to each limb. The interstimulus interval was large, variable, and self-paced by the experimenter (8–15 s) as shorter intervals could attenuate long SEP latency components (Desmedt and Manil 1970; Gibson, Brezinova, and Levene 1992; Nevalainen et al. 2015). In case the infant moved, the tap was delayed for several seconds to avoid potential modulation of the somatosensory response by the movement (Saby, Meltzoff, and Marshall 2016) and to allow movement artefacts to resolve. The sequence in which the limbs were stimulated varied across subjects. In seven neonates, it was not possible to stimulate one of the two hands because of the presence of a cannula and a reduced amount of stimuli were delivered if the baby became unsettled. This resulted in a total of 113 stimulation trains (i.e. stimulated limbs) of 6-48 stimuli (median: 18) with a median force of 246 mN (interquartile range 143 mN).

Analysis of somatosensory response

Data analysis was carried out using EEGLAB v.13 (Swartz Center for Computational Neuroscience), custom-written Matlab code and IBM SPSS version 22. Data were downsampled to 512 Hz, bandpass filtered at 1.5-40 Hz (2nd order Butterworth filter) with a 50 Hz notch filter (4th order Butterworth filter) and then epoched from -400 until +1300 ms around the stimulus. Twenty-three epochs from 18 datasets containing movement artefact were completely discarded, and 16 datasets were de-noised using independent component analysis (independent components representing (i) transient electrode ‘pop’; (ii) sinusoidal electrical interference; (iii) rapid eye movements and (iv) ECG breakthrough were
removed) (Onton and Makeig 2006). This resulted in a total of 2104 epochs analysed. Bad channels (poor contact with the scalp) were removed and then estimated with spherical interpolation as implemented in EEGLAB. All EEG epochs were baseline corrected by subtracting the mean baseline signal (-200 to 0 ms) and averaged across repetitions (i.e. each subject was characterised by a single average response per limb stimulated).

We first identified the somatosensory evoked potentials (SEPs) present following the stimulation of each limb. The grand average of the EEG responses to left hand (LH), right hand (RH), left foot (LF) and right foot (RF) stimulation across all subjects was calculated. The presence of an SEP in the grand average was determined as a significant deflection from baseline recorded at one of the pericentral electrodes (C3, C4, CP3, CP4, Cz and CPz). Significant (p < .05) deflections were identified with a point-by-point t-test in which the mean at each time-point after stimulation (variance calculated for each channel and time point across repetitions) was compared against the mean of the baseline (variance calculated for each channel across time points and repetitions).

We then investigated the emergence, and developmental changes in scalp topography and amplitude, of the detected SEPs. SEPs presence was established at subject level according to latency, prominence and topographical distribution of deflections by two observers (LF and KW). SEPs were considered present if they occurred within 80 ms of the grand average peak latency for the earlier potentials and 130 ms for the last potential (as this was less sharply defined), stood out from baseline noise and had a pericentral peak topography. The topography of each peak, when present, was then categorised as contralateral, ipsilateral or midline. The presence of each potential and of midline topography according to CGA were then assessed using a logistic regression model for hands and feet separately. In this analysis, a significant positive regression coefficient represents an increase in the occurrence of a potential or midline topography with age. The 95% confidence interval was calculated using parametric bootstrapping. The relationship between the amplitude of each potential, when present,
and CGA was tested using a linear or quadratic regression model and selecting the model with the largest F-statistic (i.e. lowest p value).

To provide a visual representation of the developmental changes in the SEPs waveform and topographical distribution of each peak, we generated average traces and scalp maps for each of four age groups (pre-term, early-term, full-term and late-term, Table 1). Average scalp maps were obtained from the scalp distributions of the peaks of each subject (not by fixing a latency). Scalp maps were normalised to their own maximum absolute voltage values.

**Results**

**Mechanical stimulation of the limbs evokes a sequence of four SEPs**

Mechanical stimulation of the left and right hand and foot consistently evoked a sequence of four SEPs: P1, N2, P2 and N3 (Figure 1). The latencies of the peaks were at approximately P100-N150-P230-N440 for the hands and at P50-N160-P240-N450 for the feet.

**The short-latency P1 potential is already established from 34 weeks CGA**

The first SEP that occurs after stimulation (P1) was consistently recorded throughout the whole study period (Figure 2 and 3) and had a clear somatotopic organization (Figure 4 and 5): contralateral following hand stimulation and at the midline following foot stimulation. P1 was recorded in 94.8% of the test occasions following hand stimulation and 87.3% following foot stimulation independently of the CGA of the infants (hands: $p = .700$; feet: $p = .117$) with a stable amplitude (hands $10.6 \pm 4.7 \mu V$: $p = .740$; feet $7.4 \pm 4.1 \mu V$: $p = .360$). When recorded, P1 was maximal contralaterally 96.4% of the
times following hand stimulation and at the midline 89.6\% of the times following foot stimulation independently of the CGA of the infants (hands: p = .320; feet p = .605).

The long-latency potentials mature over the late preterm and perinatal period

N2 was present following hand and foot stimulation from 34 weeks CGA, but there was a suggestion of a developmental shift in its topography and decrease in amplitude. N2 was recorded in 91.4\% of the test occasions following hand stimulation with a slight decrease in occurrence with age (p = .046), but never less than 75\% of the time at any given week of corrected gestation. Concurrently, there was a linear decrease in its amplitude with age from 25.0 µV before 36 weeks to 7.7 µV after 41 weeks (p < .001). N2 had a contralateral distribution 62.3\% and a midline distribution 37.7\% of the times with this proportion trending towards a significant positive association with the CGA of the infants (p = .069). N2 was recorded in 92.7\% of the test occasions following foot stimulation also with a slight, but not significant, decrease with age (p = .051) and decreased amplitude in the older infants although, unlike for the hand N2, amplitude peaked in the early-term group and then fell (quadratic model p = .032). N2 following foot stimulation had a midline topography in 94.1\% of the cases independently from the CGA of the infants (p = .352).

P2 was present following hand stimulation from 34 weeks CGA, but emerged between 34 and 42 weeks for the feet. P2 was recorded in 91.4\% of the hand stimulations independently of the CGA of the infants (p = .491), but was recorded in only 22\% of the foot stimulations before 36 weeks CGA and increased in occurrence with CGA (p = .023). However, the topography of P2 was consistently at the midline for both hands and feet throughout the study period (hands: p = .168; feet: p = .203) and its amplitude was not affected by CGA (hands (38.6 ± 2.3 µV): p = .074; feet (38.6 ± 2.4 µV): p = .100).
As with the P2, the N3 also emerged between 34 and 42 weeks CGA following foot stimulation, but, in addition, N3 had a shift in topography similar to that of N2. N3 was recorded following 86.2% of the hand stimulations independently of the CGA of the infant (p = .300), with a stable amplitude (10.9 ± 5.4 μV; p = .484), but had a distribution which was contralateral 62.0% of the times and at the midline 34.0% of the times with the proportion of midline potentials positively related to the CGA of the infants (p = .021). N3 was recorded in only 11% of the foot stimulations before 36 weeks CGA and increased in occurrence with CGA (p = .013). N3 following foot stimulation, when present, had a midline distribution (94.6%) independently of the CGA of the infants (p = .333) and its amplitude did not change with CGA (10.7 ± 5.6 μV; p = .755).

Discussion

We mapped the maturation of the hierarchical processing of tactile inputs in the developing human brain from the late preterm stage (34-36 weeks CGA) to full-term age (up to 42 weeks CGA) using somatosensory evoked potentials. We found that mechanical stimulation of hands and feet evokes a sequence of four deflections representing different levels of this hierarchy: P1, N2, P2 and N3. While the short-latency P1 (lowest processing level) is already developed at 34 weeks CGA with a characteristic somatotopic organization, the later potentials (higher processing levels) mature between 34 and 42 weeks CGA.

*Short-latency: P1*

The latency and topographical distribution of the P100 following hand stimulation and of the P50 following foot stimulation suggest an SI generator for these potentials. Intracranial recordings in adults indicate that events occurring within 110 ms after stimulation arise from SI and especially that potentials as late as 70 ms are generated in BA 3b (Truett Allison, McCarthy, and Wood 1992). In full-
term infants the P100 following hand stimulation (Karniski 1992) and MEG responses as late as 70 ms post-stimulus have been modelled as arising from the contralateral representation of the hand in SI (Pihko et al. 2005; Nevalainen et al. 2008; Saby, Meltzoff, and Marshall 2016). The P1 to foot stimulation recorded here is within the 37-50 ms range previously reported for the cortical response representing the arrival of the first afferent volley to layer IV of SI (Georgesco et al. 1982; Gilmore et al. 1987). On the other hand, the P1 following hand stimulation at 100 ms is not likely to represent the initial afferent volley, as earlier deflections can be recorded with electrical stimulation, which allows a highly synchronised, even if un-physiological, stimulation of a large amount of peripheral fibers (Handwerker and Kobal 1993; Forss, Salmelin, and Hari 1994). Here, we show that the P1 has a somatotopic organisation to stimulation of all four limbs from as early as 34 weeks. This indicates that thalamic-SI pathways for both upper and lower limbs are in place by this age, consistent with evidence of maturity of thalamic-SI tracts by 31 weeks according to post-mortem (Flower 1985; Volpe 2009) and functional EEG and MRI measures (Hrbek, Karlberg, and Olsson 1973; Pike, Marlow, and Dawson 1997; Allievi et al. 2015).

In conclusion, our data demonstrate that somatotopically organised sensory information for every limb is encoded by SI, likely Brodmann Area 3, and available for processing within higher-order brain regions from 34 weeks. This is a pre-requisite of hierarchical somatosensory processing as topographic information needs to be transferred from lower to higher centres of processing (Thivierge and Marcus 2007).

*Long-latency: N2*

Here, we showed that N2 is present from as early as 34 weeks, but it displays a trend towards a developmental shift in its topography from a purely unilateral organization in prematurity to a more midline distribution. While unilateral EEG events are generated in the corresponding hemisphere,
long-latency midline potentials are often associated with bilateral cortical sources as the electric field from both hemispheres summate at the midline, while cancelling out elsewhere (Scherg and Von Cramon 1985). The observed shift in topography for N2 is therefore likely to represent an initial immature purely contralateral response followed by an increase in the involvement of the ipsilateral hemisphere in the generation of this potential.

Our data is in line with previous estimates that the N2 at full-term age arises from bilateral post-central gyrus (Karniski 1992). While P1 is likely generated by BA 3 in SI which does not receive callosal connections even in adulthood and therefore remains a lateralised potential throughout life (Shanks, Pearson, and Powell 1985), the latency and largely symmetrical topography of N2 at term would be consistent with a source beyond BA 3, such as BA 2, which is still within SI but receives connections from the homologous region of the other hemisphere allowing a first bilateral integration (Keysers, Kaas, and Gazzola 2010). BA 2 has been shown to be bilaterally activated by somatosensory stimulation in adults: task-based fMRI studies show bilateral activation in the posterior part of SI, which includes BA 2 (Polonara et al. 1999; Nihashi et al. 2005), in agreement with the bilateral representation of digits in BA 2 in monkeys (Y Iwamura et al. 2002) and intracranial recordings in humans (T Allison et al. 1989; Noachtar et al. 1997). Our findings show a gradual emergence of this bilateral SI – BA 2 activation over the late preterm period.

In line with this hypothesis, a recent fMRI study described an increase in bilateral SI activation to somatosensory stimuli and strengthening of interhemispheric functional connectivity of this area across the equivalent of the last trimester of gestation (Allievi et al. 2015). By term equivalent age, unilateral tactile stimulation of the hand elicits contra- and ipsi-lateral BOLD responses in SI but the contralateral activation is more widespread consistent with involvement of the whole post-central gyrus (BA 3 + BA 2) compared to only area BA 2 (Erberich et al. 2006; Allievi et al. 2015). This is in line with the fact that MEG responses from ipsilateral SI are smaller than contra-laterally and detectable
only in few subjects (Korvenoja et al. 1995; Nevalainen et al. 2008) as a generator in BA 2, which sits at the top of the post-central gyrus, would have a radial orientation which is poorly detected with MEG. Functional data from rodents also show that ipsilateral somatosensory cortex becomes gradually involved from postnatal day 11 until the corpus callosum is fully mature and a bilateral somatosensory response is established between day 13-20 (Seggie and Berry 1972; Kozberg et al. 2016), equivalent to the late preterm period in humans.

The functional changes reflected by our EEG data are supported by the underlying structural maturation of callosal cortico-cortical projections over the late pre-term and perinatal period (Volpe 2009). In particular, inter-hemispheric connections between parietal cortices are facilitated by the marked increase in growth of the posterior part of the corpus callosum at about 39 weeks CGA (Rakic and Yakovlev 1968) allowing communication between these regions in the two hemispheres (Keysers, Kaas, and Gazzola 2010). Emerging involvement of the ipsilateral hemisphere, as studied with EEG, is far easier to appreciate for hand compared to foot areas because cortical representation of the two hands is relatively lateral and therefore widely spaced. However, resting-state hand and leg sensorimotor networks, captured with functional MRI, both show increasing bilateral cortical involvement from pre-term to full-term (Smyser et al. 2010).

In summary, unlike the P1 which is of consistent topography across development, the N2 reflects a clear change between the pre-term and late-term period at this second level of the somatosensory hierarchy. Further support that N2 has a separate source to P1 is the differing developmental trajectories of their amplitudes: while the P1 amplitude remains constant, the N2 amplitude is higher in the youngest infants. As BA 2 has its own body map, just like BA 3, the relatively high amplitude of the N2 in pre- and early-term infants may reflect pronounced amplification of peripheral input in BA 2, hypothesised to optimise early sensory maps formation (Shen and Colonnese 2016). Therefore, the trajectory of somatosensory function reflects anatomical milestones (Volpe 2009): 1) peripheral input
is somatotopically encoded in SI by 34 weeks, following early entry of thalamic fibres and bilateral input is integrated from full-term age after interhemispheric connections are in place. The maturation of this processing level, which allows the discrimination of bilateral tactile stimuli, occurs over the period at which birth into the extra-uterine environment is due (37-40 weeks). As this is the age at which feeding begins, during which infants typically grasp the breast with their palms (Colson, Meek, and Hawdon 2008), the ability to integrate bilateral somatosensory input would be advantageous to this end.

*Long-latency: P2*

In prematurity, foot stimulation does not elicit a clear P2, whereas hand stimulation does. The P2 is a vertex potential which have been attributed to bilateral SII in both neonates (Vaughan 1975; Nevalainen et al. 2015) and adults (Valeriani et al. 2000). Therefore the earlier development of the P2 to hand stimulation, compared to foot stimulation, could arise from faster maturation of cortico-cortical pathways from hand areas of SI to hand areas of SII. In line with this, in rat pups SI cortex is only clearly separated into columns, thus facilitating efficient outputs, for their most important body surfaces (vibrissae and forelimbs) (Armstrong-James 1975). Equivalent preferential development of upper limb somatosensory circuits is indicated in humans by the fact that, perinatally, only the paracentral gyri corresponding to hand representations are myelinated (Barkovich et al. 1988). Fine hand function is advantageous as soon as infants enter the extra-uterine environment, e.g. for breast-feeding as described above. Therefore, early maturation of upper vs lower limb somatosensory pathways may confer advantage.

Although in line with previous studies (Hrbek, Karlberg, and Olsson 1973), it may seem counterintuitive that the P2 is already maximal at the midline from 34 weeks while the N2 potential, which is generated earlier in the somatosensory hierarchy, is not maximal at the midline until 39
weeks. As midline topography of long-latency potentials is associated with activation of bilateral cortices (Scherg and Von Cramon 1985), there are two possible explanations: 1) the P2 potential reflects independent activation of both hemispheres via the thalamus, whereas the midline shift of the N2 reflects the contralateral hemisphere communicating with the ipsilateral hemisphere via later developing callosal projections 2) callosal projections between SII cortices mature earlier than between SI cortices. The former explanation is supported by the fact that SII neurons receive input from both the contralateral and ipsilateral sides of the body (Robinson and Burton 1980). The latter explanation is made plausible by the fact that, in rodents, SII cortex receives dense callosal projections just as early as SI (Wise and Jones 1976), and actually matures prior to SI cortex in terms of gene transcription (Frageul et al. 2016).

The P2 data indicate that, at later levels of the somatosensory hierarchy, upper limb circuits mature first. This indicates that early functions of somatosensory processing, such as identifying the location of input, are equally important for all four limbs. Conversely, higher-order functions such as integrating information from the two sides of the body, which facilitate important infant behaviours like bilateral grasping, mature earlier for the upper limbs.

*Long-latency: N3*

In pre-term infants the N3 is evoked by hand but not foot stimulation, reinforcing the impression that upper limb pathways within the higher levels of the somatosensory hierarchy mature earlier. However, this potential follows a similar developmental topographic shift to N2 which suggests an increasingly bilateral cortical generator and therefore an initially immature hand response too. Taken together, these findings indicate that this potential is the latest to mature which is consistent with it representing the very highest level of somatosensory processing for newborn infants. The exact cortical generator of the N3 is however unclear. The similar topographic shift to N2 suggest a shared
or nearby generator in SI. Forward projections to SII from SI are reciprocated by backward projection from SII to SI (Friedman 1983; Cauller, Clancy, and Connors 1998), so the N3 recorded here could represent a successive re-activation of the neuronal population that earlier generated the N2. This would explain its late-maturing, as feedback projections develop after feedforward ones (Berezovskii, Nassi, and Born 2011). Top-down re-activation is hypothesised to bind together parallel streams of sensory feature analysis, and predict future sensory inputs (Cauller, Clancy, and Connors 1998; Berezovskii, Nassi, and Born 2011).

Summary

There is a dynamic evolution in hierarchical somatosensory processing across the late pre-term and perinatal period. Four separate potentials comprise the neonatal somatosensory response: P1, N2, P2 and N3. The initial P1 potential is consistent with an elementary SI generator while the subsequent N2 potential is concordant with a ‘higher-level’ generator such as BA 2. Both potentials are present from 34 weeks but, while the P1 remains relatively stable, the changing topography of the N2 indicates increased involvement of the ipsilateral hemisphere in somatosensory processing. Meanwhile the P2 and N3 have a unique developmental profile with earlier maturation of processing information coming from the hands than the feet, which indicates a gradient in the maturation of the somatosensory system starting from the upper before the lower limbs. The late potentials following stimulation of the body surface could then represent a neuronal marker for higher-order somatosensory processing in late pre-term and full-term infants. Investigating how experience-dependent processes shape the development of this hierarchical somatosensory system will be an important next step in understanding why some pre-term infants develop sensorimotor difficulties.

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### Tables

#### Table 1. Demographics of the sample population divided into four age groups

|                          | Total | Pre-term | Early-term | Full-term | Late-term |
|--------------------------|-------|----------|------------|-----------|-----------|
| No. of neonates          | 34    | 9        | 9          | 8         | 8         |
| Median (range) CGA at time of study (weeks+days) | 38+1 (34+5-42+5) | 35+4 (34+5-36+4) | 37+4 (37+0-38+1) | 40+0 (39+2-40+3) | 41+5 (41+0-42+5) |
| Median (range) GA at birth (weeks+days) | 37+6 (34+2-41+4) | 35+2 (34+2-36+0) | 37+0 (35+5-38+0) | 39+5 (38+6-40+2) | 41+1 (40+2-41+4) |
| Median (range) postnatal age at study (days) | 3 (1-11) | 4 (2-5) | 3 (1-11) | 1 (1-3) | 5 (1-11) |
| Median (range) birth weight (g) | 2810 (1780-3968) | 2270 (1780-2910) | 2680 (2280-3170) | 3200 (2250-3630) | 3605 (2790-3968) |
| % males                  | 44    | 33.3     | 33.3       | 37.5      | 75.0      |
| No. multiple gestation neonates | 3      | 1        | 2          | 0         | 0         |

CGA indicates corrected gestational age; GA indicates gestational age; SD indicates standard deviation
**Figure captions**

**Figure 1**: Grand average of the EEG responses following mechanical stimulation of all four limbs. Each line is the averaged activity recorded at C4 and CP4 (red), Cz and CPz (yellow) and C3 and CP3 (blue) following stimulation of right and left hands and feet. Shading represents significant deflections (p < .05) from baseline recorded at one of these pericentral electrodes. The time of the stimulus (0 ms) is marked by a dashed vertical line. Negative and positive deflections are denoted as N and P potentials respectively, followed by a sequential number. Negative amplitudes are plotted upwards as per convention.

**Figure 2**: SEPs occurrence in response to the stimulation of the hands according to corrected gestational age (CGA) at time of study. Upper panel: illustrative mean response recorded at the midline and contralateral electrodes in four age groups (pre-term, early-term, full-term and late-term). Bottom panels: occurrence of each potential in respect to CGA and significance of the correlation. Grey dots represent mean occurrence in one-week windows (calculated only for illustrative purposes), the red solid line is the logistic regression curve and the dashed red lines delimit the 95% confidence interval.

**Figure 3**: SEPs occurrence in response to the stimulation of the feet according to corrected gestational age (CGA) at time of study. Upper panel: illustrative mean response recorded at the midline and contralateral electrodes (averaged) in four age groups (pre-term, early-term, full-term and late-term). Bottom panels: occurrence of each potential in respect to corrected gestational age and significance of the correlation. Grey dots represent mean occurrence in one-week windows (calculated only for illustrative purposes), the red solid line is the logistic regression curve and the dashed red lines delimit the 95% confidence interval.

**Figure 4**: Development of the topographical distribution of the SEPs in response to the stimulation of the hands. Upper panel: illustrative mean topographical distribution within four age groups (pre-term, early-term, full-term and late-term). The color scale is normalised to the maximum absolute voltage value within each map. Bottom panels: occurrence of midline topographies in respect to corrected gestational age (CGA) at time of study for each potential and significance of the correlation. Grey dots represent mean occurrence of the midline
topography in one-week windows (calculated only for illustrative purposes), the red solid line is the logistic
regression curve and the dashed red lines delimit the 95% confidence interval.

**Figure 5:** Development of the topographical distribution of the SEPs in response to the stimulation of the feet.
Upper panel: illustrative mean topographical distribution within four age groups (pre-term, early-term, full-term and late-term). The color scale is normalised to the maximum absolute voltage value within each map. Bottom panels: occurrence of midline topographies in respect to corrected gestational age (CGA) at time of study for each potential and significance of the correlation. Grey dots represent mean occurrence of the midline topography in one-week windows (calculated only for illustrative purposes), the red solid line is the logistic regression curve and the dashed red lines delimit the 95% confidence interval.

**Figure 6:** Summary of the emergence and hemispheric involvement for the SEPs representing the different stages of the somatosensory hierarchy for hands and feet stimulation. On the right hand side, possible generators of each potential are summarised.
Figure 2

Hands stimulation

Age Groups:
- pre-term
- early-term
- full-term
- late-term

Graph showing the occurrence (%) of different age groups over different CGA (weeks) with p-values for each graph.
Figure 3

Feet stimulation

AGE GROUPS
pre-term
early-term
full-term
late-term

5 μV

0

-400 -200 0 200 400 600 800 1000 1200

Occurrence (%)

p = .117

p = .051

p = .023

p = .013

CGA (weeks)

CGA (weeks)

CGA (weeks)

CGA (weeks)
Figure 5
Figure 6