Clinical Neurophysiology 128 (2017) 647–655

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Corticokinematic coherence as a new marker for somatosensory afference in newborns

Eero Smeds [a,*], Sampsa Vanhatalo [b], Harri Piitulainen [a], Mathieu Bourguignon [a,c], Veikko Jousmäki [a,d,e], Riitta Hari [a,f]

[a] Department of Neuroscience and Biomedical Engineering, Aalto University, PO Box 12200, 00076 Aalto, Espoo, Finland
[b] Department of Clinical Neurophysiology, Children's Hospital, HUS Medical Imaging Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[c] BCBL, Basque Center on Cognition, Brain and Language, 20009 San Sebastian, Spain
[d] Aalto NeuroImaging, Aalto University, PO Box 12200, 00076 Aalto, Espoo, Finland
[e] NatMEG, Department of Clinical Neuroscience, Karolinska Institutet, 171 77 Stockholm, Sweden
[f] Department of Art, Aalto University, PO Box 31000, 00076 Aalto, Helsinki, Finland

ARTICLE INFO

Article history:
Accepted 5 January 2017
Available online 29 January 2017

Keywords:
Corticokinematic coherence
Electroencephalography
Human
Neonatal
Proprioception
Somatosensation

HIGHLIGHTS

- We analyzed coherence between EEG and passive finger and wrist movements in newborns.
- In all newborns, EEG of the contralateral central scalp was coherent with the movements.
- Passive movements could be used to assess somatosensory function in neonatal intensive care.

ABSTRACT

Objective: Somatosensory evoked potentials have high prognostic value in neonatal intensive care, but their recording from infants is challenging. Here, we studied the possibility to elicit cortical responses in newborns by simple passive hand movements.
Methods: We examined 13 newborns (postnatal age 1–46 days) during clinically indicated 19-channel electroencephalography (EEG) recordings in the neonatal intensive care unit; EEG indications included birth asphyxia and suspected epileptic seizures. The experimenter moved the infant's wrist or fingers at 1 or 2 Hz for 5–10 min, separately on both sides. We measured movement kinematics with an accelerometer attached to the infant's hand and computed coherence between the EEG and acceleration signals (corticokinematic coherence, CKC).
Results: Statistically significant CKC (amplitude 0.020–0.511) with characteristic scalp topography was observed in all infants at twice the movement frequency. CKC was contralaterally dominant on the central scalp (median laterality index 0.48 for right-hand and −0.63 for left-hand movements).
Conclusions: Passive movements elicit cortical responses that can be readily observed in clinical EEG recordings from newborns in the intensive-care environment.
Significance: CKC is a novel, noninvasive marker for the somatosensory system. Its robustness and practical ease make it attractive for bedside assessment of neurologically compromised newborns.

1. Introduction

Improving early neurological care and later neurodevelopmental outcomes of infants with perinatal adversities is a key challenge (Marlow et al., 2005; Robertson and Finer, 1993) that would greatly benefit from practical and objective bedside methods for an early assessment of various aspects of the newborn's brain function. Somatosensory evoked potentials (SEPs) offer a reliable and robust method to address the functionality of afferent somatosensory pathways, and several recent studies suggest that SEPs can provide very early prediction of the outcome, for example, in hypoxic–ischemic encephalopathy (for reviews, see Kontio et al., 2013; Majnemer and Rosenblatt, 1996). However, the conventional method based on electric stimulation of the infant's median nerve

* Corresponding author. Fax: +358 9 470 23182.
E-mail addresses: eero.smeds@helsinki.fi (E. Smeds), sampsa.vanhatalo@helsinki.fi (S. Vanhatalo), harri.piitulainen@aalto.fi (H. Piitulainen), mabourgu@ulb.ac.be (M. Bourguignon), veikko.jousmaki@aalto.fi (V. Jousmäki), riitta.hari@aalto.fi (R. Hari).

http://dx.doi.org/10.1016/j.clinph.2017.01.006
1388-2457/

requires considerable technical expertise, thus limiting the practical availability of SEPs to only few neonatal intensive care units (NICUs) (Vanhatalo and Lauronen, 2006).

Recent magnetoencephalographic (MEG) studies on healthy adults have demonstrated that somatosensory afference can be studied reliably also using a much simpler stimulation method: continuous passive movements. Cortical signals from the primary sensorimotor (SMI) cortex entrain to the movement pace, leading to measurable corticokinematic coherence (CKC) (Bourguignon et al., 2011, 2012; Piitulainen et al., 2013b, 2015). Whereas cortical somatosensory responses to electric nerve stimulation reflect mixed somatosensory input with both tactile and proprioceptive contributions, adult studies suggest that CKC represents mainly proprioceptive afference with only a minor tactile contribution (Bourguignon et al., 2015; Piitulainen et al., 2013b).

In the present study, our aim was to find out whether CKC can be detected reliably already in newborn infants. We carried out the recordings in the most demanding conditions, that is, in the noisy NICU environment as a part of clinically-indicated electroencephalography (EEG) recordings. Notably, this context would also have the highest clinical demand for CKC-based somatosensory assessment. To provide suggestions for future clinical work, we examined technical and practical requirements that would validate the utility of CKC as a part of clinical care.

2. Methods

The recordings were performed during clinically indicated EEG measurements in the NICU of the Children's Hospital of Helsinki University Hospital. This study was part of a project that develops novel diagnostics at the Department of Children's Clinical Neurophysiology, approved by the relevant Ethics Committee of the Children's Hospital.

2.1. Patients

We here present data from 13 patients (8 boys, 5 girls; gestational ages at birth from 31 + 1 to 41 + 6 weeks + days; postnatal age 1–46 days). A 14th infant had to be excluded due to deterioration of the EEG signals by excessive restlessness caused by her jitteriness after a hypoxic-ischemic insult. The most common indications for the EEG recordings in the group were birth asphyxia and suspected epileptic seizures. One infant (P11) suffered from Erb's paresis on the left side and another (P12) from clonus on the right side. The other infants did not show lateralized symptoms. Table 1 presents relevant details of the included infants.

2.2. Movement stimulation

A clinical neurophysiologist (co-author SV) moved the infant's hands during routine EEG recordings while the infant was asleep. The stimuli were unilateral, continuous, regular extension–flexion movements of all fingers or the palm, flexing at the metacarpophalangeal level or at the wrist, respectively. Fig. 1 shows the stimulation setup (see also Supplementary Video 1). The on-line accelerometer signals on the EEG display (Supplementary Fig. S1) gave the necessary visual feedback to help the experimenter maintain a sufficiently steady stimulation rhythm. In total, we were able to perform 36 stimulation runs (2–4 per infant), each with 5–10 min of movement at either 1 or 2 Hz. For one infant (P10), only the right hand could be stimulated due to extensive bandage covering the left hand. In the other infants, both hands were stimulated in separate runs. Table 1 summarizes the measurements for each infant.

2.3. Recordings

2.3.1. EEG

EEG signals were recorded with a NicoletOne™ EEG system (Natus Medical Inc., Pleasanton, CA, USA) and 19 sintered Ag/AgCl electrodes attached to an EEG cap (Waveguard™, ANT Neuro, Enschede, Netherlands). The recording passband was 0.053–500 Hz and the sampling rate 2000 Hz. EEG signals were acquired with reference to the Cz electrode.

2.3.2. Somatosensory evoked potentials (SEPs)

As part of the clinical EEG recordings, SEPs were gathered from 9/13 infants. The median nerve was stimulated with 0.2-ms constant-current pulses delivered once every 2 s for ~10 min per side using a battery-powered portable electrical peripheral-nerve stimulator (ENERGY Light integrated stimulator, Micromed, Mogliano Veneto, Italy). The stimuli were delivered at the wrist with a pair of small disk electrodes separated by 2–3 cm (Supplementary Fig. S2). Stimulus intensity (range 9–25 mA) was individually adjusted to be just above the motor threshold. SEPs were recorded for clinical purposes and analyzed with BESA® Research (BESA GmbH, Gräfelfing, Germany). They were used in the current study only as additional neurophysiological data, and we will not elaborate on the details of their analysis (interested readers are referred to Nevalainen et al., 2015).

2.3.3. Acceleration

A 3-axis accelerometer (ADXL335 iMEMS Accelerometer, Analog Devices Inc., Norwood, MA, USA) with dedicated, in-house-made (Aalto NeuroImaging, Aalto University, Espoo, Finland), battery-powered electronics was used to record the kinematics of the passive movements. The accelerometer was attached to the infant's fingers that were firmly bound together with the sensor using elastic bandage. Acceleration signals were recorded on additional polygraph channels in the EEG data set, using the same passband and sampling rate as for the EEG signals.

2.4. Data preprocessing

2.4.1. EEG

Co-author SV, experienced in pediatric EEG, visually examined the EEG data and annotated major movement artifacts. Artifacts contaminated 0–127 s (mean 30 s) of the individual stimulation runs, thus leaving 4–10 min of clean data for the analysis. To improve spatial specificity of the EEG signals and to avoid the global influence of a single reference channel, we transformed the EEG from the Cz-referential recording to current-source-density representation with the spherical-spline surface-Laplacian algorithm (Perrin et al., 1989, 1990) as implemented by Kayser and Tenke (2006a,b). This procedure was considered appropriate as we did not attempt to model the sources of the EEG signals. All subsequent computations were performed on these transformed EEG signals.

2.4.2. Acceleration

First, acceleration signals were high-pass filtered at 0.5 Hz. Then, the Euclidean norm of the three orthogonal acceleration signals—representing the magnitude of acceleration—was computed to obtain one orientation-independent acceleration signal for the CKC analysis (Bourguignon et al., 2011). We chose to use the Euclidean norm as the orientation of the accelerometer varied slightly during the stimulation due to, for example, spontaneous position changes of the infants.

Table 1
Summary of patient information and EEG, SEP, and CKC results.

Patient	GA (w + d)	PNA (d)	EEG indication	EEG finding	SEP finding	Movement stimulation	Sleep stage	CKC
P1	39 + 6	6	Hypoglycemia, suspected seizures	Mild background abnormality; no asymmetry or focal findings	Normal	L 1 Hz R 1 Hz	Mixed Mixed	+ +
P2	38 + 3	18	Asphyxia, suspected seizures	Moderate background abnormality; no asymmetry or focal findings	Not done	L 1 Hz R 1 Hz	AS AS	+ +
P3	38 + 3	29	Post-resuscitation state	Normal	Normal	L 1 Hz R 1 Hz	AS AS	+ +
P4	40 + 0	5	Myoclonus	Mild background abnormality; no asymmetry or focal findings	Normal	L 1 Hz L 2 Hz R 1 Hz	Mixed Mixed QS	+ + +
P5	41 + 1	9	Suspected seizure	Normal	Normal	L 1 Hz R 1 Hz	Mixed Mixed	+ –
P6	31 + 1	46	Unexplained desaturations	Moderate background abnormality and asymmetry (reduced amplitudes on the right); no seizures	Not done	L 1 Hz L 2 Hz R 1 Hz R 2 Hz	Mixed AS QS QS	+ + – +
P7	40 + 5	40	Meningitis	Mild background abnormality; no asymmetry or focal findings	Not done	L 2 Hz R 1 Hz R 2 Hz	AS AS AS	+ + +
P8	40 + 2	1	Birth asphyxia	Normal	Normal	L 2 Hz R 1 Hz R 2 Hz	Mixed AS QS	+ + +
P9	37 + 6	3	Apneas, suspected seizures	Moderate background abnormality and asymmetry (spikiness on the left); no seizures	Not done	L 1 Hz L 2 Hz R 1 Hz R 2 Hz	AS QS AS AS	+ + + +
P10	41 + 6	4	Birth asphyxia	Moderate background abnormality; no asymmetry or focal findings	Normal	R 1 Hz R 2 Hz	QS Mixed	+ +
P11	40 + 4	4	Birth asphyxia, left side Erb's paresis	Moderate background abnormality and asymmetry (spikiness on the left, lower amplitudes on the right); no seizures	Right hand normal; left hand delayed and attenuated	L 2 Hz R 1 Hz R 2 Hz	AS QS Mixed	+ + +
P12	41 + 5	2	Right side clonus	Moderate background abnormality and asymmetry (abnormal waveforms posteriorly on the left); no seizures	Normal	L 2 Hz R 2 Hz	AS AS	+ +
P13	37 + 5	4	Birth asphyxia	Mild background abnormality and asymmetry (immature waveforms on the right); no seizures	Normal	L 1 Hz L 2 Hz R 1 Hz R 2 Hz	AS AS Mixed QS	+ + + –

GA = gestational age at birth (weeks + days), PNA = postnatal age at recording (days), AS = active sleep, QS = quiet sleep, Mixed = alternating active and quiet sleep. *Movement stimulation* column indicates side and frequency of the movement stimulation; e.g. L 1 Hz = left-hand stimulation at 1 Hz.

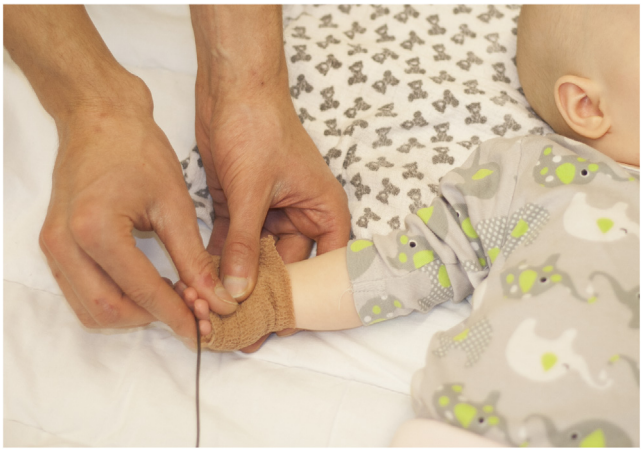

Fig. 1. Stimulation setup. The experimenter is moving the right-hand fingers of the infant. The accelerometer is attached to the fingers with bandage, and its black cable is visible. The situation was set up for illustrative purposes only, and the infant in the picture did not participate in the study.

2.5. Data analysis

2.5.1. CKC analysis

We computed the CKC between EEG signals and hand kinematics following the formulation of Halliday et al. (1995). As a part of the CKC analysis, we first determined the optimum epoch length (in number of movement cycles) that yielded statistically significant CKC at movement frequency (F0) or its first harmonic (F1) with the least amount of data. We here concentrated only on F0 and F1 as CKC typically peaks at these frequencies in adult MEG recordings (Bourguignon et al., 2011, 2012; Piitulainen et al., 2013b, 2015). Practically, CKC was computed at F0 and F1 using 10 different epoch lengths, corresponding to 1–10 movement cycles, with 80% epoch overlap. Epochs overlapping with the annotated artifact periods were excluded from the analysis. For the 10 epoch lengths and 2 frequencies, we evaluated CKC and its statistical significance as a function of the number of epochs (~amount of data) included in the analysis. At group level, the data length, at which CKC turned and remained statistically significant (hereafter referred to as the required data length), was the shortest when the analysis was performed with epochs of 2 movement cycles (median of individual optimum epoch lengths). Thus, in the final

analysis, the CKC was estimated using the whole-length data, split into epochs of 2 s and 1 s for 1-Hz and 2-Hz movements, respectively.

Both in the epoch-length optimization and in the final CKC analysis, surrogate data were used to evaluate the statistical significance of the CKC values (Faes et al., 2004). We created 1000 Fourier-transform-surrogate acceleration signals maintaining the same power spectrum as in the original signal, but replacing the phase of Fourier coefficients with random values between $-\pi$ and π. We then computed coherence between these surrogate acceleration signals and the original EEG signals and extracted, for each surrogate, the maximum coherence value across 6 contralateral and midline central EEG channels (Fig. 2A), covering the SMI cortex, and 2 frequency bins, one at F0 and the other at F1. The threshold of statistically significant coherence corresponding to $p < 0.05$ was obtained as the 95-percentile of the cumulative density function of the maximum coherence values across the 1000 repetitions. For further analyses, we extracted, from each run, the CKC peak value across the preselected channels and frequencies, as well as the required data length to obtain statistically significant CKC.

To examine hemispheric lateralization of the CKC, we calculated—separately for left- and right-hand movements—the laterality index $LI = (CKC_{left} - CKC_{right})/(CKC_{left} + CKC_{right})$ where CKC_{left} and CKC_{right} refer to CKC peak values (across 3 channels near the central area and 2 frequencies F0 and F1) in left and right hemispheres, respectively; here positive and negative LI values refer to left- and right-hemisphere dominance, respectively.

2.5.2. Analysis of sleep stages and background EEG

To explore the influence of brain state on CKC, we examined the effects of *(a)* sleep stage and *(b)* occipital background activity on the CKC peak value and the required data length. Co-author SV visually classified the infants' sleep stages in each stimulation run into either active sleep, quiet sleep, or a mixture of them both. The effects of sleep stage on the peak CKC and the required data length were evaluated with the Kruskal–Wallis test. Occipital background activity was characterized as the power ratio between slow (0.5–4 Hz) and fast (5–10 Hz) frequencies in the occipital channels (O1 and O2). The aim of this analysis was to examine whether background activity at the CKC frequencies affects the results. The slow frequencies (< 4 Hz) are a prominent component of the newborn EEG, and their amplitude varies markedly depending on the current brain state. We chose to focus on the occipital channels where the slow activity is strongest; moreover these channels are far from the SMI area activated by the simultaneous somatosensory input. We evaluated, using Spearman's rank correlation, the link between the occipital slow/fast ratio and the peak CKC as well as the required data length.

2.5.3. Analysis software

All data were preprocessed and analyzed with custom-made scripts in MATLAB® (MathWorks, Natic, MA, USA) unless stated otherwise. Apart from the surrogate analysis of CKC results, statistical analyses were performed with IBM SPSS Statistics 22 (IBM, Armonk, NY, USA).

3. Results

3.1. Practical remarks

All infants were sleeping during most of the EEG sessions, which lasted on average 83 min (range 51–131 min; $N = 13$), and all passive movements were performed during the sleep episodes. The targeted minimum of 5 min continuous stimulation was readily doable but some advance planning was required in each case to ensure that the position was comfortable for the infant as well as for the experimenter. Flexion of the infant's fingers often triggered a forceful grasping reflex, which was avoided when the experimenter took a firm hold of the infant's palm with his left hand,

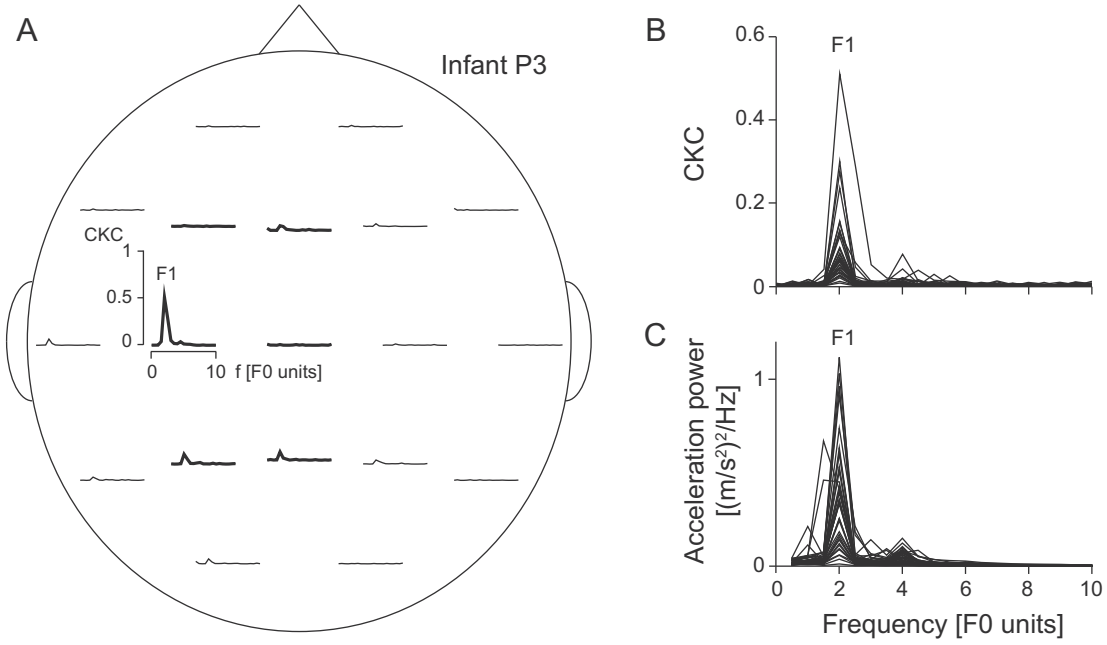

Fig. 2. CKC and acceleration spectra. (A) CKC spectra of one representative infant from all EEG channels during right-hand movements at 1 Hz. The traces of the preselected 6 channels are plotted with a thicker stroke. The most prominent peak occurs at F1 (2 times the movement frequency) in the left central channel. Smaller peaks are visible in the surrounding channels. (B) CKC spectra from all infants and all stimulation runs ($N = 36$). The traces represent the EEG channel with highest CKC peak value across the preselected 6 contralateral/midline central channels and 2 frequencies (F0 and F1). Note that in A and B, frequency is scaled to F0 units so 1 on the *x*-axis corresponds to the movement frequency (F0) and 2 corresponds to the first harmonic frequency (F1). (C) Power spectra of the acceleration signals (Euclidean norm taken across the three orthogonal directions) from all infants and all passive movement stimulations ($N = 36$).

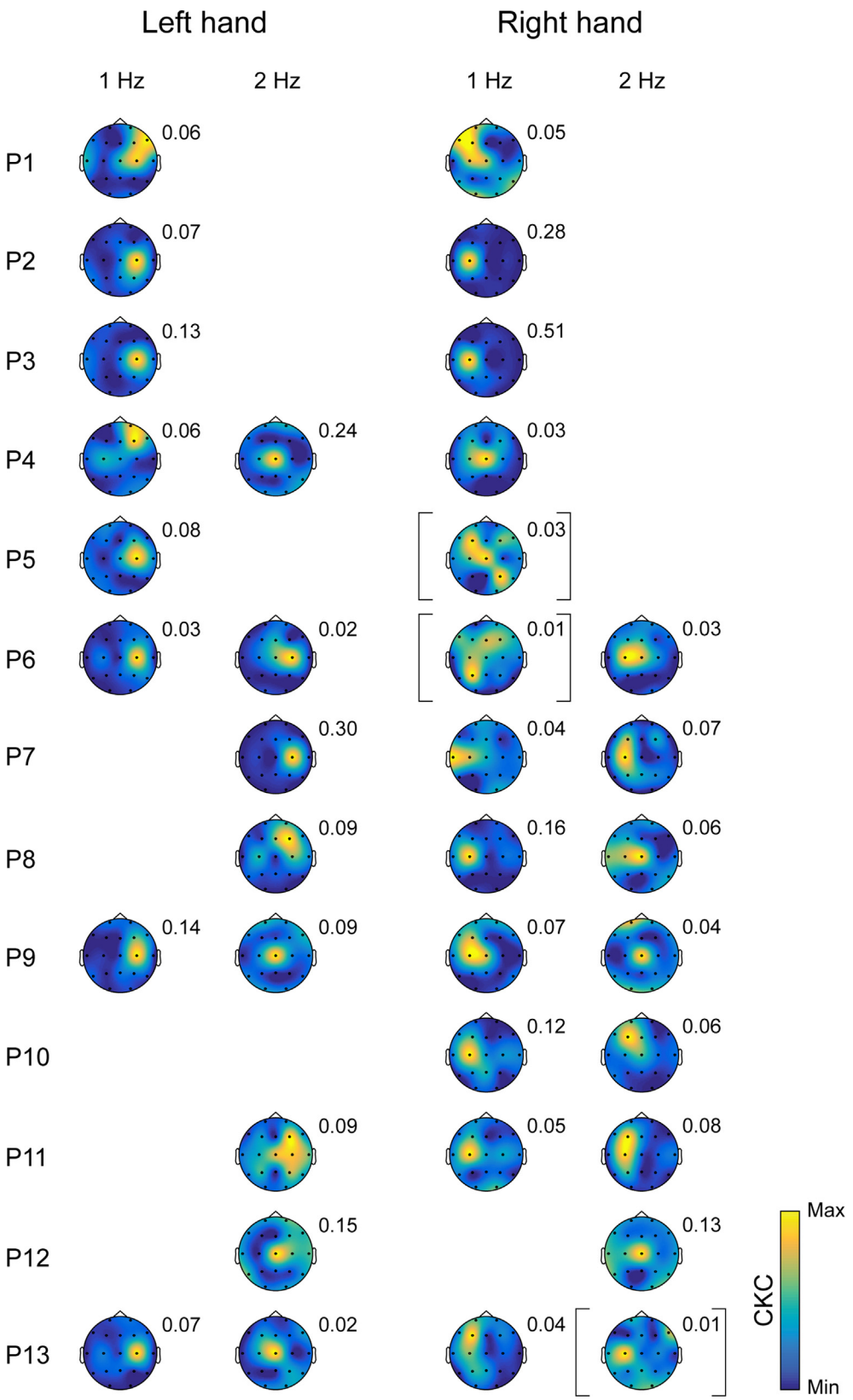

Fig. 3. Distribution of CKC at F1 in each individual measurement ($N = 36$). CKC peaks on the contralateral side with respect to the stimulated hand, mostly in the central area. Maximum CKC values are indicated next to the plots. Cases where CKC did not reach statistical significance are shown in brackets. Note that color scales are adjusted separately for each plot. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

while moving the infant's fingers (bound with the bandage together with the accelerometer sensor) with his right hand (Fig. 1 and Supplementary Video 1).

3.2. Movement characteristics

The actual stimulation frequencies were very close to the targeted ones: The power of the original single-axis accelera tion—corresponding to the spatial axis along which the movement was most prominent—peaked at 0.99 ± 0.04 Hz (mean ± standard deviation; $N = 20$) for 1-Hz movements and 2.00 ± 0.01 Hz ($N = 16$) for 2-Hz movements. Of notice, the spectra of the Euclidean norm of the acceleration signals peaked mostly at twice the movement frequency (F1; Fig. 2C). This observation is explained by the insensitivity of the (always positive) Euclidean norm to the direction of acceleration, resulting in two (positive) peaks of acceleration for each movement cycle.

3.3. CKC

Fig. 2A shows the coherence spectrum of one infant (P3) at all electrodes during right-hand 1-Hz stimulation. The highest CKC peak occurred at F1 (2 times the movement frequency) over the contralateral central area. The spatial distributions of CKC at F1 were largely similar also in the other infants, so that prominent coherence was consistently observed in the contralateral central area and its surroundings (bolded channels in Fig. 2A). Fig. 2B shows the superimposed CKC spectra of all 13 infants and stimulation runs ($N = 2$–4 per infant, total $N = 36$) from the maximum channel within the predefined area. CKC was statistically significant ($p < 0.05$) in all 13 infants and in 33 out of the total 36 stimulation runs (see Table 1). In those 33 cases, the maximum CKC value across the preselected 6 channels and 2 frequencies (F0 and F1) was 0.067 (median; range 0.020–0.511) and it occurred always at F1. At F0, in contrast, CKC was statistically significant only in 4 infants in 4 individual stimulation runs, with a range of maximum CKC values of 0.009–0.021.

The individual topographic CKC maps in Fig. 3 show that CKC was stronger in the contralateral than in the ipsilateral hemisphere. The contralateral dominance of CKC was reflected also in the laterality index (LI) values (Fig. 4): The LI was −0.63 (median; range from −0.87 to 0.33; $N = 16$) for left-hand movements and 0.48 (from −0.02 to 0.92; $N = 20$) for right-hand movements.

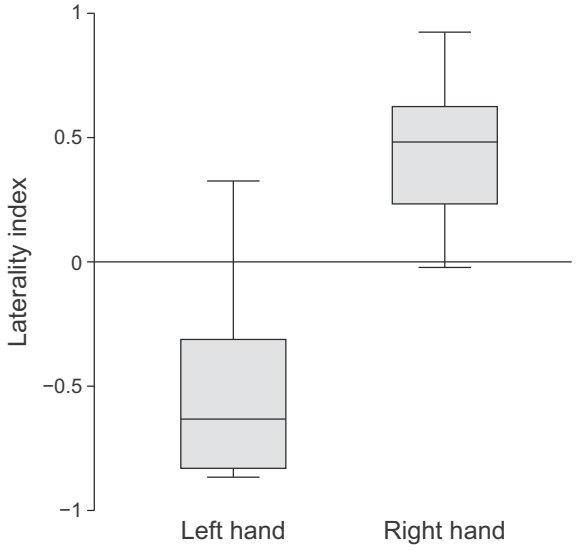

Fig. 4. Laterality index (LI) of CKC peak values during left- and right-hand stimulation. Negative LI indicates right-hemisphere dominance and positive LI left-hemisphere dominance. The box plot illustrates the median and 1st and 3rd quartiles with the T-bars indicating the total range. This figure includes data from all stimulation runs, also from those that did not show statistically significant CKC.

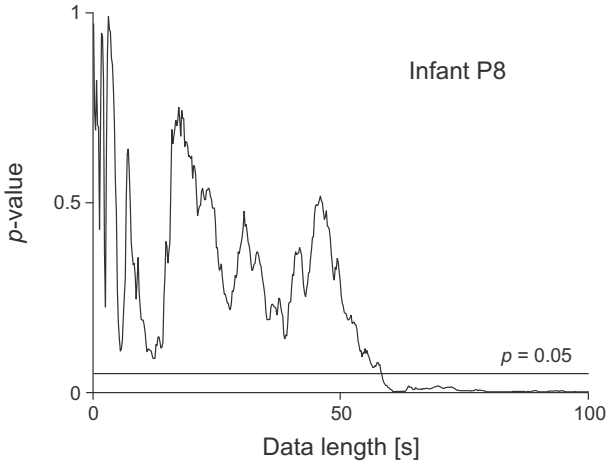

Fig. 5. Effect of data length on the p-value of the CKC in one infant, right-hand stimulation at 2 Hz. The first 100 s are shown from the total measurement duration of 323 s. The level of statistical significance (at $p = 0.05$) is reached with ~60 s of data.

Fig. 5A shows, for one representative infant (P8) and stimulation run (right-hand movement at 2 Hz) how increasing the amount of analyzed data improved the statistical significance of the CKC. In this measurement, statistical significance ($p < 0.05$) was obtained with ~60 s of data. In the whole group, the median required data length was 73 s (range 7–371 s; $N = 33$).

As a further index of corticokinematic coupling, we computed phase-locking value (PLV) between the Euclidean norm of the acceleration signals and the band-pass-filtered EEG signals. PLV yielded very similar results (data not shown) as CKC, which was expected because both measures represent the consistency of the phase difference between two signals. The main difference between the methods is that PLV removes the effect of signal amplitude, whereas coherence gives more weight to episodes of higher amplitude.

3.4. Functional brain state and its effect on CKC

We assessed sleep stage and occipital slow/fast ratio as markers of the infants' functional brain state. From the total of 36 measurements, 17 contained only active sleep, 8 only quiet sleep, and 11 both active and quiet sleep (see Table 1). Fig. 6A and B show that the CKC peak value and the required data length did not differ much across the sleep stages ($p = 0.051$ and $p = 0.27$, respectively, Kruskal–Wallis test). The median power ratio of the occipital slow (1–4-Hz) versus fast (5–10-Hz) activity across all infants and stimulation runs was 11.8 (range 8.3–20.2; $N = 36$), and the peak CKC and the required data length did not depend systematically on this slow/fast ratio ($p = 0.93$ and $p = 0.59$, respectively, Spearman's rank correlation; Fig. 6C and D).

3.5. Clinical EEG and SEP findings

The EEG recordings were normal in 3 infants (see Table 1) but showed mild to moderate background abnormality in the remaining 10. The EEG of 5 infants showed some level of interhemispheric asymmetry, but also these infants showed statistically significant CKC on both sides.

SEPs were normal on both sides in 8 out of the tested 9 infants (see Table 1). In one infant (P11) who suffered from left-sided Erb's

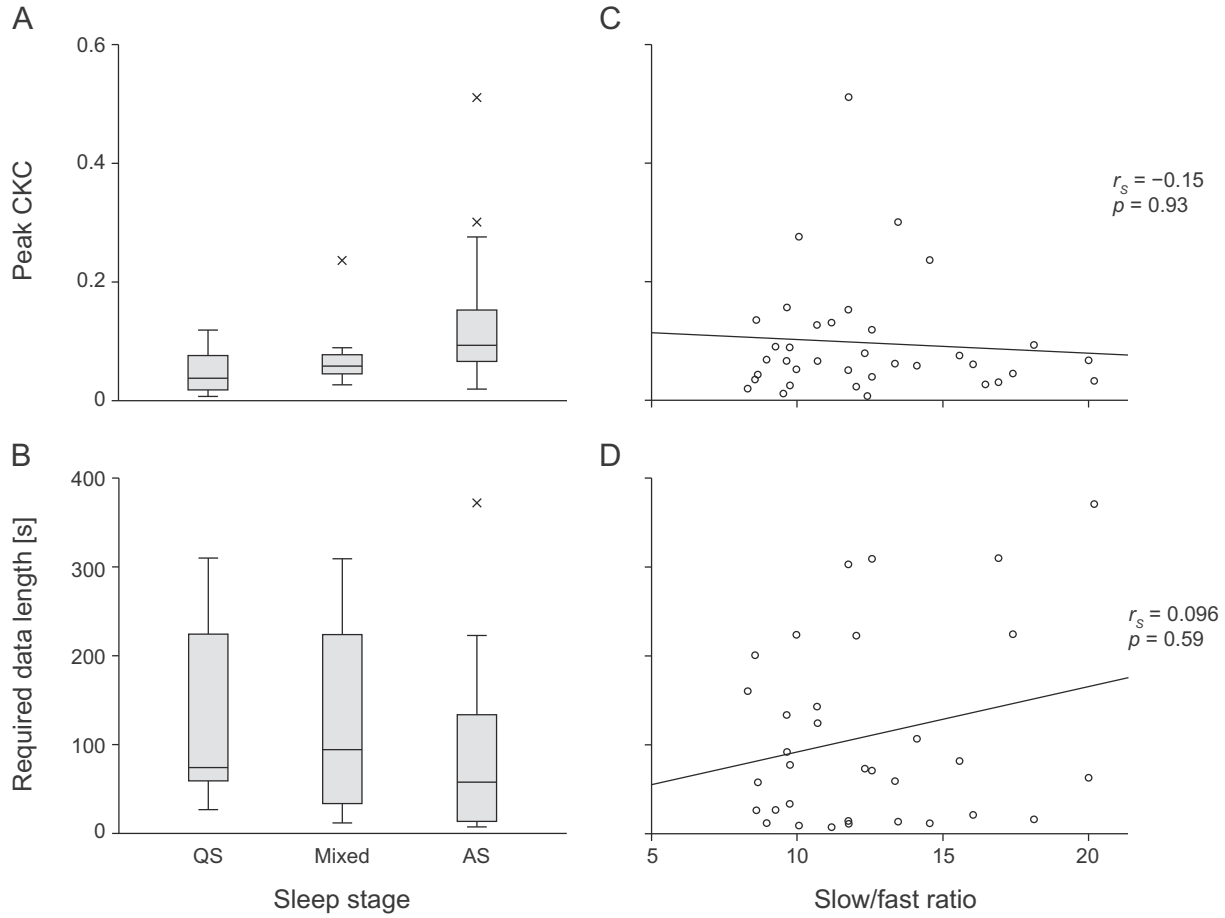

Fig. 6. Effect of the infants' brain state on CKC. Peak CKC (A) and required data length (B) at different sleep stages, with no statistically significant differences between the stages. The crosses indicate outliers beyond 1.5 interquartile ranges above the 3rd quartile. Peak CKC (C) and required data length (D) as a function of the occipital slow/fast ratio, with no statistically significant correlations. Spearman's rank correlation coefficients (r_s) and the corresponding p-values are indicated in the plots. A and C include data from all stimulation runs, whereas B and D only include runs that showed significant CKC. AS = active sleep, QS = quiet sleep, Mixed = alternating active and quiet sleep.

paresis, SEPs were normal on the left hemisphere but were delayed and attenuated on the right hemisphere. In this individual, CKC was statistically significant on both sides with approximately equal amplitudes. In another infant (P5), SEPs were normal on both sides but CKC was statistically significant only on the right hemisphere. The other 7 infants whose SEPs were tested showed normal SEPs as well as statistically significant CKC. Supplementary Fig. S3, illustrating a normal SEP to right median-nerve stimulation in one representative infant (P12), shows a scalp distribution similar to those observed for CKC (Figs. 2C and 3).

4. Discussion

We show that bedside recordings of cortical responses to passive movements are feasible in the neonatal intensive-care environment. The coupling between the movements and the infants' EEG activity, demonstrated with CKC analysis, fully agreed with previous adult MEG recordings (Piitulainen et al., 2013b, 2015). We performed our measurements in the technically challenging intensive-care environment and found CKC in all 13 studied infants. Passive-movement stimulation could thus offer a new possibility for assessing the somatosensory system in critically ill neonates.

4.1. CKC in adults and newborns

Coherence between cortical activity and peripheral movements was first demonstrated in adults performing voluntary hand movements (Bourguignon et al., 2011; Jerbi et al., 2007; Kelso et al., 1998; O'Suilleabhain et al., 1999; Piitulainen et al., 2013a; Pollok et al., 2004). More recent studies have shown that CKC is found at similar levels during both active and passive movements indicating that it represents afferent signaling from the periphery to the cortex (Bourguignon et al., 2015; Piitulainen et al., 2013b). CKC is easily detected in all healthy adults, mainly in the contralateral SMI area (Bourguignon et al., 2011; Jerbi et al., 2007; Piitulainen et al., 2013b, 2015).

The current results in newborn infants are well in line with these findings in adults. The strongest CKC was typically found in the contralateral central area; however, some spatial variability was observed, possibly related to the immature cortical organization (Lauronen et al., 2006; Nevalainen et al., 2008; Pihko et al., 2009). In the current study, CKC was strongest at F1 (twice the movement frequency), agreeing with a previous adult study using similar methodology (Piitulainen et al., 2013b). That CKC peaked at F1 and not at F0 likely pertains to that signals from the SMI cortex track the absolute velocity of movements rather than the velocity itself, being thus insensitive to movement direction itself (O'Suilleabhain et al., 1999). Indeed, in the present study, the flexion and extension phases of the movements had close-to-opposite acceleration profiles (Supplementary Fig. S1). The stimulation thus caused 2 similar positive deflections per movement cycle both in the brain signals and in the Euclidian norm of the acceleration (which is also independent of the direction), leading to power accumulation at F1 in both signals.

In adults, CKC occurs during both active and passive movements, regardless of the level of concomitant tactile input (Bourguignon et al., 2015; Piitulainen et al., 2013b), and it thus mostly reflects afferent signaling from peripheral proprioceptors. The situation is different for SEPs, which rely on direct stimulation of nerve trunks at the periphery so that the relative contribution of different fibers depends on the intensity of the electric stimulation. Nevertheless, both CKC and SEPs represent the flow of somatosensory information from the periphery to the cortex, which is of high interest in neonatal intensive care.

4.2. Clinical feasibility and future prospects

Early functional assessment of the somatosensory system has proven valuable in guiding neurological care in the NICU (Majnemer and Rosenblatt, 1996; Nevalainen et al., 2015). However, the conventional SEP recordings have been applied routinely in only few units because of technical challenges with the electric nerve stimulation, data quality, and SEP analysis. Reliable electric stimulation of the median nerve—without causing excessive discomfort to the infant or stimulation artifacts into the EEG signals—is an especially demanding step in these measurements.

Several features of CKC make it attractive as a new marker for somatosensory function. First, it is based on passive-movement stimulation, which is noninvasive and simple to perform. Second, our data indicate that robust CKC can be obtained from as little as ~1 min of stimulation, and that the results are not very sensitive to the infant's sleep stage or background EEG activity. Finally, the CKC analysis is based on spectral properties at the stimulation frequency and its harmonics, which are clearly below the frequencies of typical NICU noise, such as power-line and muscle artifacts (for a review of artifacts, see André et al., 2010). Thus, the method is resilient to artifacts that often severely compromise traditional SEP recordings.

The current study shows the general applicability of CKC measurements in the NICU. However, large prospective studies are still required to clarify some remaining questions. The method failed in 3 out of 36 stimulation runs, which could be due to insufficient measurement length, environmental noise, stimulation irregularities, or genuine pathophysiological abnormalities. The current data do not allow distinction between these alternatives. Furthermore, we observed some apparent discrepancies in our comparison of the CKC results and the clinical data: Lateralized abnormalities in the conventional EEG/SEP findings were not associated with clear laterality in the CKC results. These differences might be in part explained by technical issues, such as slight variability in the manually-generated movement stimulation impeding interhemispheric comparison of CKC values.

In future studies, the stimulation setups can be standardized by replacing the manual stimulation with an automatic passive-movement stimulator. Such devices have already been utilized in CKC recordings in adults (Piitulainen et al., 2015) as well as in functional magnetic resonance imaging studies in newborn infants (Allievi et al., 2013; Arichi et al., 2010). Automatized stimulation would improve the stability of both movement frequency and amplitude both within and between subjects, which would be critical especially for longitudinal studies and follow-ups. A passive-movement stimulator for neonates, however, still needs to be validated for safety, patient comfort, and clinical efficiency.

The key aim of future studies is to explore, in detail, the clinical diagnostic utility and physiological relevance of CKC in newborns. These studies should characterize CKC levels in distinct groups of neonatal patients, as well as in healthy control subjects, with a proper comparison with results from other tests. It will also be important to systematically assess whether CKC—unlike SEPs (Pihko and Lauronen, 2004)—is indeed independent of the infant's sleep stage, as suggested by the current results. Finally, prospective follow-up studies are required to demonstrate the prognostic value of CKC, for example, in predicting later cerebral palsy and other neurological disorders associated with neonatal hypoxic–ischemic brain damage. We expect that passive-movement stimulation combined with CKC analysis could then transform into a valuable new tool to be used in the neurophysiological assessment of newborn patients in the NICU.

Acknowledgements

This work was supported by the Academy of Finland (grant numbers #266133 and #296240 to HP; grant numbers #288220 and #276523 to SV), the Louis-Jeantet Foundation, Geneva, Switzerland (RH), the Emil Aaltonen Foundation, Tampere, Finland (ES), and the Research Programs Unit of the Faculty of Medicine of the University of Helsinki (ES). The funding sources were not involved in the study design, in the collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit the article for publication. The authors contributed to the study as follows: All authors participated in designing the study, in analyzing and interpreting the data, and in writing the manuscript. SV collected the data. All authors have approved the final article. We thank Helge Kainulainen at Aalto NeuroImaging and Anton Tokariev and Marita Suni at the University of Helsinki for valuable help.

Conflict of interest: None of the authors have potential conflicts of interest to be disclosed.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2017.01.006.

References

Allievi AG, Melendez-Calderon A, Arichi T, Edwards AD, Burdet E. An fMRI compatible wrist robotic interface to study brain development in neonates. Ann Biomed Eng 2013;41:1181–92. http://dx.doi.org/10.1007/s10439-013-0782-x.

André M, Lamblin MD, d'Allest AM, Curzi-Dascalova L, Moussalli-Salefranque F, Nguyen The Tich S, et al. Neurophysiol Clin/Clin Neurophysiol Neurophysiol Clin 2010;40:59–124. http://dx.doi.org/10.1016/j.neucli.2010.02.002.

Arichi T, Moraux A, Melendez A, Doria V, Groppo M, Merchant N, et al. Somatosensory cortical activation identified by functional MRI in preterm and term infants. Neuroimage 2010;49:2063–71. http://dx.doi.org/10.1016/j.neuroimage.2009.10.038.

Bourguignon M, De Tiège X, Op de Beeck M, Pirotte B, Van Bogaert P, Goldman S, et al. Functional motor-cortex mapping using corticokinematic coherence. Neuroimage 2011;55:1475–9. http://dx.doi.org/10.1016/j.neuroimage.2011.01.031.

Bourguignon M, Jousmäki V, Op de Beeck M, Van Bogaert P, Goldman S, De Tiège X. Neuronal network coherent with hand kinematics during fast repetitive hand movements. Neuroimage 2012;59:1684–91. http://dx.doi.org/10.1016/j.neuroimage.2011.09.022.

Bourguignon M, Piitulainen H, De Tiège X, Jousmäki V, Hari R. Corticokinematic coherence mainly reflects movement-induced proprioceptive feedback. Neuroimage 2015;106:382–90. http://dx.doi.org/10.1016/j.neuroimage.2014.11.026.

Faes L, Pinna GD, Porta A, Maestri R, Nollo G. Surrogate data analysis for assessing the significance of the coherence function. IEEE Trans Biomed Eng 2004;51:1156–66. http://dx.doi.org/10.1109/TBME.2004.827271.

Halliday DM, Rosenberg JR, Amjad AM, Breeze P, Conway BA, Farmer SF. A framework for the analysis of mixed time series/point process data—theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. Prog Biophys Mol Biol 1995;64:237–78. http://dx.doi.org/10.1016/S0079-6107(96)00009-0.

Jerbi K, Lachaux J-P, N'Diaye K, Pantazis D, Leahy RM, Garnero L, et al. Coherent neural representation of hand speed in humans revealed by MEG imaging. Proc Natl Acad Sci USA 2007;104:7676–81. http://dx.doi.org/10.1073/pnas.0609632104.

Kayser J, Tenke CE. Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: i. Evaluation with auditory oddball tasks. Clin Neurophysiol 2006a;117:348–68. http://dx.doi.org/10.1016/j.clinph.2005.08.034.

Kayser J, Tenke CE. Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: ii adequacy of low-density estimates. Clin Neurophysiol 2006b;117:369–80. http://dx.doi.org/10.1016/j.clinph.2005.08.033.

Kelso JAS, Fuchs A, Lancaster R, Holroyd T, Cheyne D, Weinberg H. Dynamic cortical activity in the human brain reveals motor equivalence. Nature 1998;392:814–8. http://dx.doi.org/10.1038/33922.

Kontio T, Toet MC, Hellström-Westas L, van Handel M, Groenendaal F, Stjerna S, et al. Early neurophysiology and MRI in predicting neurological outcome at 9–10 years after birth asphyxia. Clin Neurophysiol 2013;124:1089–94. http://dx.doi.org/10.1016/j.clinph.2012.12.045.

Lauronen L, Nevalainen P, Wikström H, Parkkonen L, Okada Y, Pihko E. Immaturity of somatosensory cortical processing in human newborns. Neuroimage 2006;33:195–203. http://dx.doi.org/10.1016/j.neuroimage.2006.06.041.

Majnemer A, Rosenblatt B. Evoked potentials as predictors of outcome in neonatal intensive care unit survivors: review of the literature. Pediatr Neurol 1996;14:189–95. http://dx.doi.org/10.1016/0887-8994(96)00049-5.

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. http://dx.doi.org/10.1056/NEJMoa041367.

Nevalainen P, Lauronen L, Sambeth A, Wikström H, Okada Y, Pihko E. Somatosensory evoked magnetic fields from the primary and secondary somatosensory cortices in healthy newborns. Neuroimage 2008;40:738–45. http://dx.doi.org/10.1016/j.neuroimage.2007.09.075.

Nevalainen P, Rahkonen P, Pihko E, Lano A, Vanhatalo S, Andersson S, et al. Evaluation of somatosensory cortical processing in extremely preterm infants at term with MEG and EEG. Clin Neurophysiol 2015;126:275–83. http://dx.doi.org/10.1016/j.clinph.2014.05.036.

O'Suilleabhain PE, Lagerlund TD, Matsumoto JY. Cortical potentials at the frequency of absolute wrist velocity become phase-locked during slow sinusoidal tracking movements. Exp Brain Res 1999;126:529–35. http://dx.doi.org/10.1007/s002210050761.

Perrin F, Pernier J, Bertrand O, Echallier JF. Spherical splines for scalp potential and current density mapping. Electroencephalogr Clin Neurophysiol 1989;72:184–7. http://dx.doi.org/10.1016/0013-4694(89)90180-6.

Perrin F, Pernier J, Bertrand O, Echallier JF. Corrigendum EEG 02274. Electroencephalogr Clin Neurophysiol 1990;76:565. http://dx.doi.org/10.1016/0013-4694(90)90009-9.

Pihko E, Lauronen L. Somatosensory processing in healthy newborns. Exp Neurol 2004;190(Suppl. 1):2–7. http://dx.doi.org/10.1016/j.expneurol.2004.01.024.

Pihko E, Nevalainen P, Stephen J, Okada Y, Lauronen L. Maturation of somatosensory cortical processing from birth to adulthood revealed by magnetoencephalography. Clin Neurophysiol 2009;120:1552–61. http://dx.doi.org/10.1016/j.clinph.2009.05.028.

Piitulainen H, Bourguignon M, De Tège X, Hari R, Jousmäki V. Coherence between magnetoencephalography and hand-action-related acceleration, force, pressure, and electromyogram. Neuroimage 2013a;72:83–90. http://dx.doi.org/10.1016/j.neuroimage.2013.01.029.

Piitulainen H, Bourguignon M, De Tiège X, Hari R, Jousmäki V. Corticokinematic coherence during active and passive finger movements. Neuroscience 2013b;238:361–70. http://dx.doi.org/10.1016/j.neuroscience.2013.02.002.

Piitulainen H, Bourguignon M, Hari R, Jousmäki V. MEG-compatible pneumatic stimulator to elicit passive finger and toe movements. Neuroimage 2015;112:310–7. http://dx.doi.org/10.1016/j.neuroimage.2015.03.006.

Pollok B, Gross J, Dirks M, Timmermann L, Schnitzler A. The cerebral oscillatory network of voluntary tremor. J Physiol 2004;554:871–8. http://dx.doi.org/10.1113/jphysiol.2003.051235.

Robertson CM, Finer NN. Long-term follow-up of term neonates with perinatal asphyxia. Clin Perinatol 1993;20:483–500.

Vanhatalo S, Lauronen L. Neonatal SEP – Back to bedside with basic science. Semin Fetal Neonatal Med 2006;11:464–70. http://dx.doi.org/10.1016/j.siny.2006.07.009.