A critical period of Corticomuscular and EMG-EMG coherence detection in 9-25 week old healthy infants

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Key Points:

- The early postnatal development of functional corticospinal connections in human infants is not fully clarified.
- Corticospinal drive to upper and lower limb muscle show developmental changes with an increased functional coupling in infants between 9-25 weeks in the beta frequency band.
- The changes in functional coupling coincide with the developmental period where fidgety movements are present in healthy infants.
- Data support a possible sensitive period where functional connections between corticospinal tract fibres and spinal motoneurones undergo activity-dependent reorganization.

Abstract:

The early postnatal development of functional corticospinal connections in human infants is not fully clarified. We used EEG and EMG to investigate the development of corticomuscular and intramuscular coherence as indicators of functional corticospinal connectivity in healthy infants aged 1-66 weeks. EEG was recorded over leg and hand area of motor cortex. EMG recordings were made from right ankle dorsiflexor and right wrist extensor muscles. Quantification of the amount of corticomuscular coherence in the 20-40 Hz frequency band showed a significantly larger coherence for infants aged 9-25 weeks compared to younger and older infants. Coherence between paired EMG recordings from Tibialis anterior muscle in the 20-40 Hz frequency band was also significantly larger for the 9-25 week age group. A low amplitude, broad-duration (40-50 ms) central peak of EMG-EMG synchronization was observed for infants younger than 9 weeks, whereas a short-lasting (10-20 ms) central peak was observed for EMG-EMG synchronization in older infants. This peak was largest for infants in between 9-25 weeks. These data suggest that the corticospinal drive to lower and upper limb muscles shows significant developmental changes with an increase in functional coupling in infants aged 9-25 weeks, a period which coincides partly with the developmental period of normal fidgety movements. We propose that these neurophysiological findings may reflect the existence of a sensitive period where the functional connections between corticospinal tract fibres and spinal motoneurones undergo activity-dependent reorganization. This may be relevant for the timing of early therapy interventions in infants with pre- and peri-natal brain injury.

Abbreviations: CA, corrected age; CP, Cerebral Palsy; EEG, electroencephalography; EMG, electromyography; TA, Tibialis anterior muscle;

Introduction

Human infants develop a number of sophisticated motor skills within the first few years of their life. The ability to perform precise, goal-directed movements using the extremities has been shown to depend on the integrity of corticospinal connections to spinal motoneurones (Lemon 2008, Lemon et al 1998). Although probably primarily evolved for precise control of the fingers of primates, direct corticomotoneuronal connections are found for all muscles that have so far been investigated in humans (Petersen et al 2003, Rothwell et al 1991). In addition to their importance for voluntary muscle activation, corticospinal pathways also play a role in the control of movements that are traditionally thought to be highly automatic such as gait and respiration (Adams et al 1989, Barthelemy et al 2011, Petersen et al 2012). Furthermore, there is now strong evidence that the corticomotoneuronal system plays a pivotal role in motor learning and in the maintenance of motor skills (Dayan & Cohen 2011, Pascual-Leone et al 2005).

The early development of the corticospinal system is well-documented in rat, cat and monkey (Clowry 2007, Martin et al 2007). In these species, functional connections are not fully developed until after birth (Clowry 2007, Martin et al 2007). Therefore, it has been hypothesised that functional connections between corticospinal tract fibres and spinal motoneurones in humans occurs relatively late during the first year of life, possibly just prior to the appearance of independent use of the fingers at around one year of age, similar to what is seen in non-human primates (Eyre 2003). However, histochemical investigation of the corticospinal tract in spinal cords from human foetuses and new-borns coupled with the measurement of muscular potentials evoked by transcranial magnetic stimulation (TMS) in infants in the age range 26 weeks to 12 months post conceptual age has indicated that corticospinal fibres may be in weak functional contact with spinal motoneurones already prior to birth (Eyre et al 2000). Recent studies have also documented that infants are capable of independent finger movements, precision grip and goal-directed movements already from around 3-4 months of age (Wallace & Whishaw 2003).

In kittens, Martin and co-workers (Martin et al 2007) have provided evidence of a critical period in the development of the corticospinal tract between the first and second month following birth. In this period, the previously exuberant corticospinal connections undergo activity-dependent re-organisation and pruning such that only functional connections survive and non-functional connections are removed (Martin et al 2007). This is particularly evident

in the disappearance of many of the ipsilateral corticospinal pathways during the first and second post-natal months. This process of pruning can be halted through functional or behavioural inactivation of the crossed corticospinal pathways causing the ipsilateral pathways to persist into adulthood. Furthermore, training in this period may enhance the connectivity between the cortex and the spinal cord and facilitate a higher degree of prehension of the paw (Friel et al 2012).

It is unknown whether exuberant corticospinal pathways exist in early human life and it is unknown whether there is a critical period during the development of the human corticospinal tract (Eyre 2003). However, unilateral pre-natal corticospinal tract lesions have been shown to be associated with the existence of abnormal fast-conducting ipsilateral corticospinal pathways (Carr et al 1993, Farmer et al 1991). This finding is likely to be the human correlate of the persistence of the ipsilateral corticospinal tract produced by contralateral corticospinal tract inactivation or lesioning in the cat (Martin et al., 2007). Of particular interest and supportive of the concept of there being a critical period in early human motor development, is the temporary emergence of so-called fidgety movements (FM). These are observed in typically developing human infants between the ages of 2 to 5 months corrected age (CA) (the baby´s age calculated from term date), and are indicative of normal supraspinal re-organization leading to establishment of purposeful goal-directed movements mediated via activity in the corticospinal tract (Guzzetta et al 2003, Hadders-Algra 2007). During a detailed motor assessment of general movements, the absence or impairment of FM is highly predictive of cerebral palsy (Bosanquet et al 2013, Darsaklis et al 2011, Hamer et al 2011) and their absence or impairment is strongly associated with lesions of the corticospinal pathways (Guzzetta et al 2003).

Non-invasive information regarding corticospinal functional connectivity can be obtained using coherence analysis of sensorimotor cortex MEG/EEG and EMG recordings acquired simultaneously. In adult subjects it can be shown that beta frequency oscillations (15-35 Hz) are coherent with similar frequencies in the contralateral motor cortex during sustained voluntary muscle contraction (Conway et al 1995, Mima & Hallett 1999, Salenius et al 1996). CMC is absent or greatly reduced in subjects with lesions of the corticospinal tract (Fang et al 2009, von Carlowitz-Ghori et al 2014). Beta frequency coherence and motor unit synchronization is present between pairs of single motor units recorded from within the same muscle or from motor units recorded during co-contraction of synergistic muscle pairs and is

also impaired or altered by central nervous system lesions (Datta et al 1991, Datta & Stephens 1990, Farmer et al 1993a, Hansen et al 2005, Nielsen et al 2008). EMG-EMG coherence and synchrony and CMC thus reflect the common oscillatory drive to the motor units from the corticospinal tract (Farmer 1998). Similar results demonstrating common drive to motoneurones are obtained for surface EMG signals recorded within muscles and between co-contracting muscles (Farmer et al 1993b, Gibbs et al 1995, Halliday et al 2003, Hansen et al 2001).

It has been demonstrated that both CMC and the coherence and synchrony between EMGs undergo developmental increases in late childhood for both arm and leg muscles (Farmer et al 2007, James et al 2008, Petersen et al 2010). Beta and gamma frequency coherence is weak for both leg and arm muscles in children around 3-5 years of age, but it increases toward adult levels in children above 10 years of age (Farmer et al 2007, James et al 2008, Petersen et al 2010). This developmental increase in oscillatory common drive is not seen in affected muscles of infants and children with a documented lesion of the corticospinal tract causing cerebral palsy (Petersen et al 2013).

Based on these findings, it is predicted that little or no CMC or EMG-EMG coherence is present in children younger than 3-4 years of age. However, a recent study has shown low level but significant CMC between vertex EEG and a leg muscle EMG in newborn infants (Kanazawa et al 2014). As the authors of this study pointed out, this finding may be consistent with the presence of functional corticomotoneuronal projections at or shortly after birth, as has been suggested from studies using TMS in neonates (Eyre 2007). In the present study, we studied the developmental changes in CMC and EMG-EMG coupling in arm and leg muscles of infants within the first year of life using cross-sectional data. We hypothesized that the period in which typically developing infants exhibit fidgety movements (FM) may be a time during which CMC and EMG-EMG coherence may be present. Furthermore, as these movements do not persist beyond the age of 6 months we hypothesized that any detectable coherence might be a transient phenomenon. Animal studies have demonstrated that central fibres discharge at specific frequencies during establishment of synaptic contacts as a competitive process where non-functional connections are removed (Favero et al 2014, Friel et al 2014, Minlebaev et al 2011). Therefore, if FM reflect activity-dependent re-organization of the corticospinal tract connectivity during a critical period for motor development, then the

detection of CMC and EMG-EMG coherence may reflect an increase in corticospinal traffic during the developmental period in which there are FM.

Methods

Ethical approval

The local ethics committee, Denmark, Region H, granted approval of the study (H-1-2014-006), and all parents provided written consent prior to participation. All experimental procedures conformed with the latest revision of the Declaration of Helsinki.

Participants

Sixty-one infants (45 term-born; 16 preterm; age range 1-66 weeks; mean age 20 weeks; 33 girls; 26 boys) participated in the study. Data from two infants had to be discarded due to poor recording quality. Age counted from term date (CA) was used for all infants. The preterm infants (n=16) were all born at a gestational age (GA) of 28+0 – 32+6 weeks. Both term-born and preterm infants were neurologically healthy and typically developing. Electroencephalography (EEG) and electromyography (EMG) were performed during a session when the infants also had a General Movements Assessment (GMA) to determine the presence or absence of Fidgety Movements (FM).

Experimental design

Each experimental session was only commenced when the infant was fed, satisfied and alert to ensure a good quality of the different recordings. One of the infant's parents was present during each individual recording.

General Movements Assessment (GMA)

Infants younger than 25 weeks were video-recorded for 5 minutes while lying in prone position on a mattress. The environment was free from distracting visual or auditory stimuli, and the infant did not use a pacifier. The infant wore only a body stocking so that the joints of the extremities were fully visible. Videos of the infants' movements were recorded using the Microsoft Kinect (Microsoft, USA) camera and data was stored on a PC for off-line analysis by a clinician trained in the use of GMA. Since FM´s are only present when typically-developed infants are 2-5 months of age, we did not include video recordings for children above the age of 25 weeks (Einspieler et al. 2004).

Electroencephalographic (EEG) and electromyographic (EMG) recording

EEG and EMG were recorded simultaneously for 10-15 minutes with the infant either lying in prone position or sitting on a mattress. The baby was placed as comfortably as possible, but in a position where we could promote muscle activity in the targeted muscles. If insufficient spontaneous muscle activity occurred, the experimenters encouraged the child to move by tickling them under the feet, or having them grasp towards an object with their hands. If unhappy, the infant was comforted by a parent and/or a pacifier. In such situations, additional recording time was added. EMG activity was recorded from the right leg using two sets of custom-made bipolar electrodes with small recording areas (9 mm^2) and a short bi-polar inter-electrode distance (0.5 cm). The pairs of bipolar electrodes were placed at the most proximal and distal ends of the right Tibialis anterior (TA) muscle, respectively. The distance between each of the pair of EMG electrodes was 5-10 cm apart (depending on the age of the child). All infants underwent EMG recordings from the TA muscle. Twenty-five of the infants also underwent additional EMG recordings from the right wrist extensor muscles using the same custom-made electrodes as for the leg. One pair of electrodes was placed over the lateral aspect of the forearm 1-2 cm distal to the elbow joint. Since the sensitivity of coherence analysis depends on the amount of EMG activity recorded, it was ensured that the EMG electrodes for both the leg and arm were placed so that signals of at least 10-20 μV were recorded (Keenan et al 2012). The skin was prepared by first brushing the skin softly with sandpaper (3M red dot; 3M, Glostrup, Denmark). EEG was recorded from 13 electrodes on the scalp using one of three, differently sized infant EEG-caps according to head circumference. Electrode gel was used to secure proper conduction. All signals were sampled by eemagine EEG 3.3.0.6. Electrode impedance was kept below 5 kOhm. Data was sampled at 625 Hz, filtered (band-pass, 3 Hz–200Hz), and stored on a PC for off-line analysis.

Offline data analysis

Signal processing and analysis were performed off line. All data were imported into Matlab (Mathworks, Massachusetts, USA) for further analysis.

Frequency and time domain analysis

Frequency domain analysis of the data was undertaken using the methods set out in detail by (Halliday et al 1995). For EEG-EMG coherence analysis periods with no EMG activity or significant artefacts or noise were removed before coherence analysis was performed. This

was done by visual inspection of the data and selection of episodes of EMG activity lasting longer than 10 s and with mean amplitude larger than 3 times baseline noise. This resulted in datasets with a total duration of approximately 5-6 minutes in all infants. Full wave rectification of surface EMG signals was applied. This approach has been shown to maximize the information regarding timing of motor unit action potentials (MUAP) whilst suppressing information regarding MUAP waveform shape (Boonstra & Breakspear 2012, Halliday & Farmer 2010, Myers et al 2003, Ward et al 2013). As a precursor to undertaking coherence, synchronization, phase and subsequently population analysis of the data, the EMG signals were normalized to have unit variance (Halliday & Rosenberg 2000). For EEG-EMG coherence analysis, the EEG and the rectified normalised EMG signals are assumed to be realisations of stationary zero mean time series denoted by x and y.

For EMG-EMG coherence analysis we generated one point process time series for each EMG recording by triggering on the largest non-rectified EMG spike activity in each recording, while preventing triggering on large artefacts (Fig. 1). This was done in order to minimize the influence of cross-talk in the calculation of coherence between the two electrodes and is similar to the approach, which has been used and validated in a number of previous studies (Farmer et al 1998, Gibbs et al 1995, Gibbs et al 1997, Hansen et al 2001, Hansen et al 2000). Two trigger levels were applied: The first was adjusted to 1.25 X the mean amplitude of the EMG activity, whereas the second level was adjusted to 1.75 X the mean amplitude of the EMG activity. Only EMG activity with amplitudes falling within this window generated a point in the respective point process. These thresholds were selected since they minimized possible cross-talk as much as possible, while still allowing more than 2000 points in each point process within the recording period, which was necessary in order to produce coherence estimates with a reasonably low variability (see Farmer et al. 1993a). The times of occurrence of the EMG triggered pulses were recorded and used to create the two point-process time series for coherence and cumulant density function analysis. These two point processes are assumed to be realizations of stationary zero mean time series, denoted by x and y.

The results of analysis of individual records generated estimates of the auto-spectra of the either the EEG and EMG or the two EMG spike trains $fxx(\lambda)$, $fyy(\lambda)$, and their cross-spectra $fxy(\lambda)$. We then estimated three functions that characterize the signals' correlation structure: coherence, $|R_{xy}(\lambda)|^2$; phase, $\varphi_{xy}(\lambda)$; and cumulant density, $q_{xy}(u)$. Coherence estimates are

bounded measures of frequency association between the signals and are defined over the range [0, 1]. The time domain cumulant density estimate of synchrony between the signals is not bounded. The phase between the signals is defined over the range [$-\pi$, $+\pi$]. For the present data, coherence estimates provide a measure of the fraction of the activity in one signal at any given frequency that can be predicted by the activity in the second signal. In this way, coherence estimates quantify the strength and range of frequencies of common oscillations that are either shared between the EEG and the EMG or shared between two EMGs. The timing relations between the EEG and EMG or between two EMG signals are estimated from the phase. The cumulant density, calculated from the inverse Fourier transform of the cross-spectrum, provides an unbounded time-domain representation of the EEG-EMG or the EMG-EMG correlation structure analogous to the cross-correlogram and thus captures both correlation and timing information between signals (Halliday et al 1995).

Note on EMG Thresholding and Cross-talk minimisation.

Because of cross-talk we report EMG-EMG coherence using the point process method. The times of occurrence of motor unit spikes were determined by thresholding the EMG signals and using MATLAB to assign a time of occurrence to each data point. This method has been used in a number of other studies and it reliably detects common drive to pools of motor neurones in both the time and the frequency domains (Farmer et al 1998, Gibbs et al 1995, Gibbs et al 1997, Hansen et al 2001, Hansen et al 2000). This approach also has similarities to that adopted by Farina et al (2013) in which the cumulative spike train is constructed from individually identified motor units and then analysed in the frequency domain. In contrast to Farina et al. (2013), we were unable to identify individual motor units and superimposition effects will therefore be present in the calculations. Because thresholding detects the largest motor units i.e. those closest to the recording electrode, it is more resistant to the effects of cross talk when compared to estimating coherence and synchronization using the whole rectified EMG signal. However, smaller motor units might be indirectly influential on the detected time of occurrence of a larger motor unit i.e. the larger unit that might have escaped detection may as a result of superimposition cross the threshold. Such a mechanism could lead to inclusion of cross-talk within the calculation of point process coherence albeit at a much lower level than if the whole EMG had been used. Preliminary analysis of the data showed that point process and whole EMG analysis produced compatible results: coherence

peaks in the same frequency ranges and motor unit synchronization in the time domain. The rectified EMG-EMG analysis, however, showed additional coherence across the whole range of frequencies-this additional coherence and the distorting effects of cross-talk was markedly reduced through use of the threshold method. The threshold approach is helpful due to the small size of the babies' muscles and the necessity of placing the electrodes in relatively close vicinity to each other. Coherence based on the two point processes generated from thresholding the EMG showed coherence within restricted frequency bands. The phase over the range of significant coherence showed a delay consistent with the physiological delay between motor units recorded from different areas of the muscle. The phase outside the beta frequency band was, in contrast to the non-threshold data, random. The cumulant density and the central peak in the cumulant density constructed from thresholded EMGs showed an appearance and time course consistent with previous studies of motor unit synchronization. The coherence, phase and cumulant results from thresholded EMG data are therefore consistent with physiological EMG synchronization rather than zero lag volume conducted cross-talk and consequently it is this data that we report.

We did not threshold the EMG signals for the calculation of EEG-EMG coherence. There were two reasons for this. First, there is no risk of cross-talk between EEG and EMG recordings. Second, we wish to compare like with like i.e. EEG data analysis requires the whole signal and therefore a waveform based coherence and cumulant analysis for both EEG and EMG is the preferred approach.

Pooled estimates provide a single time or frequency domain measure that describes the correlation structure across a number of data sets (Amjad et al 1997). Like individual coherence estimates, pooled coherence estimates provide a normative measure of linear association on a scale from 0 to 1 (Halliday & Rosenberg 2000). Similarly, pooled cumulant density estimates provide a measure of the time-domain correlation across a number of records.

The interpretation of pooled estimates of spectrum, phase, coherence and cumulant is similar to those obtained for individual records, except any inferences relate to the population as a whole. Details of pooled coherence analysis and on setting of confidence limits can be found in (Amjad et al 1997). The approach used here to calculate pooled coherence estimates was to pool individual coherency estimates (Farmer et al 2007, Halliday & Rosenberg 2000). The

individual coherency estimate for record *i* was denoted as $R_{xy}^{i}(\lambda)$, where this has been calculated from L_i segments of data. This coherency function is a complex quantity, and the corresponding coherence is its magnitude squared. The pooled coherence across *k* records, at frequency λ is then:

$$\left| \frac{\sum_{i=1}^{k} L_i \, R_{xy}^{i}(\lambda)}{\sum_{i=1}^{k} L_i} \right|^2$$

Estimates of the above pooled coherence provide a single parameter describing the correlation structure, as a function of frequency, within the *k* records in a single population. This can be considered analogous to single coherence estimate calculated from $\sum_{i=1}^{k} L_i$ segments of data.

Estimates of pooled coherence, pooled spectra, pooled cumulant density functions and pooled phase were used to summarize the EEG-EMG correlation estimates and the EMG-EMG correlation estimates in each age group of subjects. Estimates of pooled coherence provide a single parameter describing the correlation structure as a function of frequency, within the records of a single population, where the total number of records to be used equates to the number of subjects for each group.

Statistics

The cumulated sum of the logarithmic values of EEG-EMG and EMG-EMG coherence in the 20-40 Hz frequency range were collected and plotted as a function of corrected age of the infants. This is similar to previous studies in which coherence has been quantified and was used to ensure normal distribution of data (Kristeva et al 2007, Willerslev-Olsen et al 2015). Age-related changes in the amount of coherence were modelled using best fit regression analysis. The significance level was adjusted to 0.05 using the equation:

$$1 - (0.05)^{1/(L-1)}$$

Adjusted correlation coefficients were used to determine the best model for each of the data sets. One-way ANOVA was used to determine significant differences between specific age groups of infants (1-8 weeks, 9-25 weeks, >25 weeks). Holm-Sidak was used as PostHoc test. All values are given as mean ± 95 % confidence intervals. All analyses were performed with Sigmaplot 12.5 **(**SYSTAT Software, San Jose, CA, USA**)** for Windows.

Results

Video analysis of general movement (GM) and fidgety movements (FM)

The video recording was of insufficient quality to determine the presence or absence of Fidgety movement (FM) in four of the infants in the developmental age range where FM are expected (9-25 weeks). FM were observed in all the remaining infants within that age range. EEG and EMG data were used from all infants including the four in whom good quality video was not obtained.

EEG-EMG coherence

Fig. 1A-D illustrates coherence for a paired EEG recording from Cz and an EMG recording from the right TA muscle in an individual 10-week-old infant. Significant coherence between the two recordings was observed in a frequency band from 20 to 40 Hz (Fig. 1B) accompanied by structure in the cumulant density with a negative peak at a lag around 15 ms. Similar significant CMC was observed in 10 of the 59 infants. Infants with significant CMC were all in the age range 6-30 weeks. When quantifying the logarithmic amount of coherence in the 20-40 Hz frequency band (taking the average value of the coherence between the EEG recording and the two EMG recordings from the TA for each individual infant) an age-related pattern in the coherence was observed with the highest levels of coherence detected for infants aged 6-30 weeks (Fig. 1D). When applying non-linear regression analysis to this dataset the best fit was found for a four parameter Gaussian distribution (Fig. 1D, thick full line; f = -1.75+0.33*exp(-.5*((x-9.38)/7.15)^2); Converged fit result: 91 %; adjR^2=0.28; F=9.3; p<0.0001). The maximum value of this distribution was found at 9.4 weeks.

In order to further investigate the age distribution of EMG-EMG coherence, the infants were divided into three age groups: 1-8 weeks, 9-25 weeks and >25 weeks. The middle of these age groups roughly covers the period where FM are observed in typically-developing infants. One-way ANOVA showed a significant interaction between groups (F=6.78; p=0.002) and

postHoc Holm-Sidak test showed a significantly lower coherence in the infants >25 weeks than in the other two groups ($p<0.01$).

[Insert Fig. 1 here]

In order to investigate whether CMC localised over the leg area of the primary sensorimotor cortex CMC amplitude spatial analysis was performed. CMC was calculated for all 13 EEG electrodes in the 10 infants in whom significant coherence was observed. In Fig. 1E the scalp amplitude distribution of mean coherence across subjects is shown. CMC amplitude has been colour coded and plotted across the scalp recording sites. The Cz electrode site is shown for guidance. It is seen from this spatial analysis that the coherence localises to the Cz electrode and electrodes immediately frontal to Cz. This scalp region corresponds to the midline leg area of the sensorimotor cortex.

EEG from the C3 scalp electrode (corresponding to the hand/arm area of the left sensorimotor cortex) and simultaneously recorded right wrist extensor EMG was used to estimate CMC in 25 infants (Fig. 2). A relationship between the presence of CMC and subject age was also found for EEG-EMG data recorded from the C3 EEG electrodes and the contralateral arm muscle EMG. Significant coherence was found in six of the 25 infants. Four of these infants were in the age range 9-25 weeks, whereas the last two were 30 and 35 weeks, respectively. Data from one of the infants in the 9-25 weeks group is shown in Fig. 2B-C. It can be seen that the coherence and cumulant density functions are very similar to those observed for the coupling between Cz and TA EMG, except there is a shorter lag for the negative peak in the cumulant density function (approximately 7 ms). The age distribution of the logarithmic amount of coherence was also found to be best fitted by a four parameter Gaussian distribution (Fig. 2D, thick full line; f = -1.72+0.51*exp(-.5*((x-21.6)/2.59)^2); Converged fit result: 97 %; adjR^2=0.24; F=3.6; $p<0.05$). The maximum value for the distribution was found at 21.6 weeks. One-way ANOVA showed no difference between infants 1-8 weeks (n=3), 9-25 weeks (N=9) and >25 weeks (n=11; p=0.2)

[Insert Fig. 2 here]

Scalp localisation of CMC for the right forearm extensor muscles was determined through spatial analysis. Calculation of the magnitude of coherence between each of the 13 EEG electrodes and the EMG recording from the right wrist extensors in the 6 infants with significant coherence revealed the scalp distribution of CMC shown in Fig. 2E. It is seen that the maximal of the mean coherence of the 6 subjects was observed for electrodes placed left of the midline and posterior to the inter auricular line i.e. contralateral to the activated right arm muscles and close to but slightly posterior to the C3 electrode which in adults is generally over the hand area of the left sensorimotor cortex.

TA EMG-EMG coherence

Coherence between EMGs recorded from two bi-polar electrodes over the TA muscle was also calculated. In order to minimize the risk of cross-talk between the paired recordings, all EMG recordings were converted into spike trains by identifying EMG potentials within a narrow window of discrimination set to capture the largest ongoing EMG activity in each of the two EMG recordings (Fig. 3A). Despite this approach cross-talk was detected in 11 children through the presence of significant coherence over all frequencies and a large very narrow central peak in the cumulant density function. Data from these children were discarded from further analysis, leaving data from 48 children.

[Insert Fig. 3 here]

Fig. 3B-C show analysed data from a 14-week-old infant. EMG-EMG coherence was observed in this infant's recordings peaking at around 20 Hz with significant EMG-EMG coherence between 10 and 40 Hz. In the cumulant density function calculated for the same data, a narrow central peak (at time zero) of duration of 15 ms was observed with secondary peaks to each side of the central peak at lags of approximately 50 ms. These primary and secondary peaks are consistent with motor unit synchronization and 20 Hz common oscillatory drive also reflected in the dominant coherence peak at around 20 Hz (Farmer et al 1993b).

Although EMG-EMG coherence was observed in most infants at frequencies from 10 Hz similar to the infant illustrated in Fig. 3, we decided to restrict quantification of coherence in

the 20-40 Hz frequency band in order to make the analysis comparable to the analysis of EEG-EMG coherence. Calculation of the logarithmic amount of EMG-EMG coherence in the 20-40 Hz frequency band in each infant again revealed an age-distribution which was best fitted with a four parameter Gaussian function (Fig. 3D, thick full line; f = -1.27+0.46*exp(-.5*((x-15.0)/3.66)^2); Converged fit result: 99.5 %; adjR^2=0.33; F=8.6; p<0.0001). The maximum value for this distribution was found at 15.0 weeks. One-way ANOVA showed a significant interaction between infants aged 1-8 weeks (n=8), 9-25 weeks (n=25) and >25 weeks (n=15; F=12.59; p<0.001). PostHoc Holm-Sidak test showed that infants in the age group 9-25 weeks had significantly larger coherence than the younger (p<0.01) and older infants (p<0.001).

Fig. 4 shows the pooled coherence and cumulant density function for each of these three subject populations. This confirms that infants in the age group 9-25 weeks (Fig. 4B) showed greater coherence in the 10-40 Hz band when compared to younger infants (1-8 weeks; Fig. 4A) and older infants (>25 weeks) (Fig. 4C). Notice also in the pooled cumulant data (Fig. D-F) that the youngest infants (1-8 weeks) show a low amplitude, long lasting (around 50 ms) central peak, whereas a narrower (10-20 ms) central peak was observed in the older infants (largest in the age group 9-25 weeks).

[Insert Fig. 4 here]

Fig. 5A shows that magnitude of Cz EEG-TA EMG CMC was positively correlated with the magnitude of the coherence between the TA EMG-EMG recordings (Pearson correlation coefficient: 0.7; p<0.0001). Likewise, a significant positive correlation was detected between the magnitude of Cz EEG-TA EMG CMC and the magnitude of C3 EEG-arm extensor EMG CMC (see Fig. 5B, Pearson correlation coefficient: 0.56; p<0.001). No significant coherence or synchronization was observed between simultaneous EMG recordings from TA and wrist extensor muscles in any of the infants in whom this analysis was possible.

[Insert Fig. 5 here]

Discussion

In this study, we demonstrate developmental changes in CMC and intramuscular EMG-EMG coherence that occur within the first year after birth in typically developing children. The main finding is that of high levels of primarily beta frequency range CMC and EMG-EMG coherence in infants aged 9-25 weeks CA that is either not present or is present to a lesser degree in the younger or older infants. The EMG-EMG coherence in infants aged >9 weeks is accompanied by a narrowing of the central peak of EMG-EMG synchronization when compared to the synchronization peak observed in infants aged <9 weeks. We interpret these results as reflecting changes in the central patterns of activity responsible for upper and lower limb motoneurone recruitment and suggest that the findings are related to activity within and re-organization of corticospinal connections during this developmental period.

Limitations of the study

EEG and EMG recordings in infants are technically demanding and great care has to be taken to avoid artefacts. Possible cross-talk between pairs of EMG recordings is a particular concern due to small muscle size and the correspondingly small distances between the pair of bipolar electrodes in infants. We attempted to minimize cross-talk by using very small bipolar electrodes with small recording areas and by placing the electrodes as distant from each other as anatomically possible. Furthermore, in order to focus on the motor units closest to the recording area for the EMG-EMG coherence, we analysed motor unit spikes and generated spike trains through triggering on the largest EMG potentials in each recording. Despite these procedures it cannot be ruled out that the two EMG electrodes picked up signals from the same population of motor units due to the anatomical organization of the muscles and superimposition of motor units. However, several observations from our results are not consistent with cross-talk contamination of the data. First, if cross-talk had contributed to the coherence, we would have expected to observe coherence over all frequencies rather than coherence restricted to the 10-40 Hz frequency band (Halliday et al 2003). Second and importantly, cross-talk is also difficult to reconcile with the observed age-distribution of the coherence magnitudes. This is because smaller muscle size with reduced inter-electrode distance will increase the potential for EMG cross-talk. Therefore, maximum EMG-EMG coherence would have been observed in the youngest smallest infants. This was not the case. Finally, the positive correlation between CMC (constructed from EEG, a signal that cannot be contaminated with leg muscle EMG cross-talk) and TA EMG-EMG coherence is strongly supportive of a physiological explanation for our findings. Furthermore, in subjects for whom

we obtained CMC data for both arm and leg there was a positive correlation of coherence magnitudes. This shows that beta frequency range CMC is detectable for both leg and arm muscles in some subjects, but more importantly its shows that in these subjects the inter subject differences of both leg and arm CMC amplitude scale similarly.

Several additional observations also support a physiological CMC effect. First, the negative peak in the central feature observed in the cumulant density function was shifted from zero by an average of 7 ms for the arm muscles and 15 ms for the leg muscles. A similar morphology of this EEG-EMG cumulant feature has been observed in adult CMC data (Farmer et al 2004), and the delay is consistent with conduction in a central neural pathway with a longer distance to the leg muscles than to the arm muscles. This finding cannot be explained by cross-talk or other non-physiological signals. With an estimated average distance of 45 cm between cortex and leg and 28 cm between cortex and wrist, these values would correspond to a conduction velocity of approximately 30 m/s. For comparison, Eyre et al. (Eyre et al 2000) reported a central conduction time in the corticospinal tract for neonates of around 10-20 m/s and around 60-80 m/s for adults. Second, the scalp distribution of coherence shows that the largest coherence between cortex and leg muscle corresponds to the Cz electrode, the leg area of the motor cortex; whereas the maximum CMC for the right wrist extensors was observed over the left hemisphere and posterior to the inter auricular line i.e. close to C3 which is the EEG electrode that is generally over the left upper limb sensorimotor area.

It should be noted that there are a number of other factors that will change with a baby´s age which cannot be controlled e.g. thickness of facia below the recording site; these factors through their effects on the size and duration of the EMG action potentials may affect the spectral shape of the raw and rectified EMG. Furthermore, there is debate in the literature about the effects of action potential shape and the effects of EMG rectification on the estimation of EMG spectra and EMG-EMG coherence (Farina et al 2013). Whilst there may be an uncontrolled effect of motor unit shape on coherence estimates in this data, we have focused on extracting timing information from the EMG to estimate the common drive to motor neuron pools (Halliday & Farmer 2010, Ward et al 2013).

It is also of interest that the pooled cumulant for the paired TA EMG recordings (Fig. 4) showed broad-band synchronization for children below the age of 9 weeks, whereas short-term synchrony was observed for older children. Broad-band synchrony has been attributed

to presynaptic synchronization of inputs to spinal motoneurones. Short-term motor unit synchrony can be attributed to the simultaneous arrival of inputs to pools of motoneurones from collaterals of common last order neurones (Datta & Stephens 1990, Kirkwood 2016, Kirkwood & Sears 1978, Kirkwood et al 1982). In adult humans, short-term synchronization is replaced by broad-peak synchronization following lesions of the corticospinal tract, supporting the idea that it is produced by activity in last order corticospinal inputs to the spinal motor neurone pool (Datta et al., 1991 and Farmer et al., 1993a). Our current observations may thus reflect the emergence at an age of approximately 9 weeks of more direct functional collaterals from corticospinal neurones which provide common input to separate pools of TA motoneurones.

Sixteen of the infants were born more than 4 weeks preterm and we used their CA in relation to the expected term date in the analysis of the age-distribution of coherence. This is standard procedure in developmental studies, since the time from conception (i.e. onset of development) is considered more relevant for developmental changes than the time of birth. Furthermore, the data for the preterm infants revealed a similar distribution compared to infants born at term (see Figures 1-3).

We quantified coherence in the 20-40 Hz frequency band for both EEG-EMG and EMG-EMG recordings, although coherence was observed for the EMG-EMG recordings also at lower frequencies. This was done in order to ensure comparable data, but also because it is reasonable to assume that only the higher EMG-EMG frequencies, which are also observed in the EEG-EMG coherence, reflect corticospinal activity. In this respect our data from infants are similar to data from adults where coherence in both alpha, beta and low gamma bands may be observed for EMG-EMG recordings, whereas only CMC in the ~20 Hz beta band is present in EEG-EMG recordings (Farmer 1998).

Developmental changes in CMC

Kanazawa et al. (2014) reported significant but low level CMC in a large number of newborn infants (Kanazawa et al 2014). This result may seem at variance with the small amount of CMC observed in our present study. However, the actual magnitudes of CMC observed in their study (0.005-0.011) were not different from those observed in the youngest infants in our study. The main difference between the two studies is that Kanazawa et al. (2014) accepted small peaks of coherence crossing the level of significance at any frequency from 1

to 100 Hz as evidence of significant CMC, whereas we required reproducible significant coherence over a specific range of frequencies (20-40 Hz). With this stricter frequency criterion, we observed very little CMC in the youngest infants and it did not reach statistical significance except for infants older than approximately 6 weeks and younger than approximately 25-30 weeks. Our CMC data were further supported through the observation of a similar age distribution of peak EMG-EMG beta range coherence, although a slightly different distribution of age-related coherence values was found in the non-linear regression analysis (peak coherence at 9.4 and 15 weeks respectively for EEG-EMG and EMG-EMG coherence for TA muscle). Coherence for wrist extensor muscle CMC was observed to occur at a somewhat older age that TA muscle CMC and TA muscle EMG-EMG coherence (21.6 weeks versus 9.4 and 15 weeks, respectively). It is important to note that this result was derived from only a small number of subjects. It should be noticed that EMG-EMG coherence was seen from 10-40 Hz, whereas CMC was observed only at frequencies above 20 Hz. This is in line with observations from adults where peaks of coherence are seen for EMG-EMG coherence in both the alpha and beta bands, whereas CMC is usually only observed in the beta band (Farmer, 1998). This indicates that the lower frequencies observed in the EMG-EMG coherence do not originate from the corticospinal tract.

The CMC and EMG-EMG coherence and cumulant observed in infants aged approximately 6-30 weeks in the present study suggests that there is a focused 20-40 Hz activity in the corticospinal tract during this developmental time period. In the study by Kanazawa et al., (2014) Granger causality analysis was consistent with the brain activity driving the muscle activity. Likewise, in our study the negative cumulant density feature suggests that EEG is leading the EMG (See also Farmer et al., 2004 for further discussion). We suggest that this oscillatory activity may be important in re-organization and pruning of the corticospinal connections to the spinal motoneurones, which has been shown to take place in an activity-dependent manner in other animal species soon after the establishment of functional corticospinal connections (Martin et al 2007). There is also evidence that establishment and re-organization of neural connections during development of the nervous system is regulated by oscillatory activity in the neural elements (Favero et al 2014, Friel et al 2014). Activity in the gamma range (35-60 Hz) is especially dominant in this activity-dependent regulation of synaptic growth and pruning, which overlaps at least in part with the frequency range observed in our study (Favero et al 2014, Friel et al 2014, Minlebaev et al 2011).

Is common drive related to Fidgety Movements?

The larger intramuscular EMG-EMG coherence in infants around 15 weeks CA when compared to the infants younger or older than this age also correlates with the typical developmental emergence of Fidgety Movements (FM). FM are small movements of neck, trunk and limbs of moderate speed and variable acceleration, which are present in the awake infant (Einspieler 2004). In neurologically healthy infants, FM appear at approximately 9 weeks CA and peak around 12 weeks CA. They disappear with the emergence of intentional and antigravity movements around 22-25 weeks CA. Absence or impairment of FM 9-20 weeks post term is a prognostic indicator of subsequent motor impairment and cerebral palsy (Burger & Louw 2009). It has been hypothesised that FM require an intact cortical sub-plate and its efferent motor connections (Hadders-Algra 2007). The sub-plate is vulnerable to hypoxic-ischemic damage. In humans the cortical sub-plate disappears at about the time that FM cease (~5 months after birth). Early oscillatory and synchronous activity is dependent on an intact cortical sub-plate. This early synchronous activity occurs during a critical period of normal neural development but it fades as the sub-plate undergoes regression (Luhmann et al 2009, Minlebaev et al 2011). These bursts of oscillatory activity early in development have been shown to be important in the sensory-motor co-ordination and the development of functional networks within primary motor and somatosensory cortex of neonatal rats (An et al 2014). Our data would be consistent with a transient increase in oscillatory traffic within the corticospinal tract possibly due to sub-plate activity impacting on developing motor cortex neuronal networks and their outputs. The developmental timing of this increased oscillatory activity correlates with the emergence of FM. The reduction of CMC and EMG-EMG coherence with the infant's age may correlate with a disappearance of central oscillatory drive to motoneurones as the cortical sub-plate naturally regresses.

We suggest that future studies address whether there is CMC and EMG-EMG coherence that is specific to FM themselves, and whether it is this common drive, during this developmental time period, that specifically underlies the emergence of the movements. Given that FM are an indicator of typical motor development in healthy infants and that their impairment or loss is highly predictive of the emergence of cerebral palsy, we postulate that loss of CMC and EMG-EMG coherence during this time period may be also an adverse prognostic feature in human motor development (see also results of Petersen et al., 2013 in older children with established cerebral palsy).

These data indicate that the corticospinal drive to lower and upper limb muscles shows significant developmental change, with a specific increase in functional coupling in the age group 9-25 weeks CA. We propose that this may reflect the existence of a sensitive period where the functional connections between corticospinal tract fibres and spinal motoneurones undergo activity-dependent reorganisation. This is relevant for the timing of early intervention in infants with brain lesions.

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Additional information section

Competing interest

All authors state no conflict of interest.

Author contributions

ARR, AH, XL, MDO, and JBN designed the study and in collaboration ARR, AH and MDO executed all the experiments. ARR, MDO, MWO, SFF and JBN performed the data analysis. All the authors participated in drafting the manuscript or contributed with important observations in the process of writing the manuscript. All authors approved the final version of the manuscript. All authors accept to be accountable for all aspects the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors state that all persons designated as authors qualify for authorship, and all those who qualify for authorship are listed on the manuscript.

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Figure legends

Fig. 1. Corticomuscular coherence (CMC) between Cz and TA EMG in infants 1-66 weeks corrected age (CA).

Paired EEG and EMG recordings from the Tibialis anterior (TA) muscle and the brain are illustrated in Fig 1A. B and C show CMC at different frequencies (B) and the EEG-EMG cumulant density (C). The dashed line in figure B indicates the level of 95% confidence level for the individual coherence estimate. Figures A, B and C are recordings from a single subject (10 week old infant).

The logarithm of the amount of coherence between EEG and EMG in the 20-40 Hz frequency band in the 59 children is plotted against corrected gestational age (D). The 95 % confidence level is indicated by the horizontal dotted line. The solid line is the non-linear regression for the best fit. The black dots indicate term infants and the white dots indicate preterm infants (<36 weeks of GA). The shaded grey area indicates the developmental time interval where FM are observed in typically-developing infants.

The mean magnitude of coherence determined using spatial analysis from 13 electrodes in 10 infants is represented by a 2D scalp plot (E) with the Cz electrode occupying the coordinates [0,0].

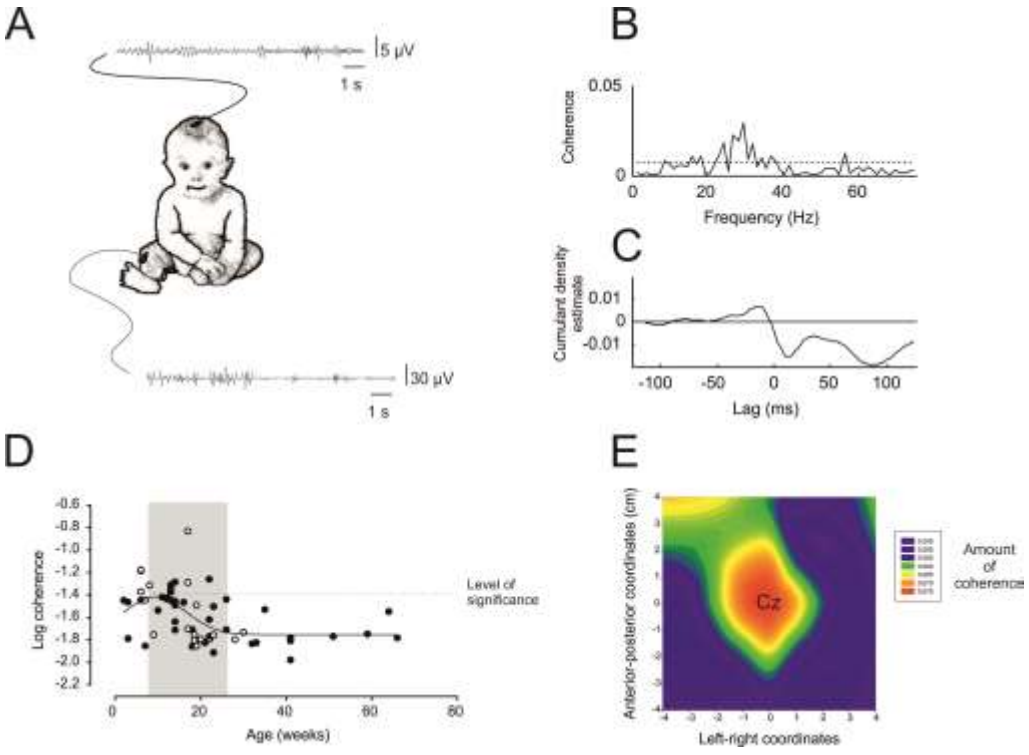

Fig. 2. Corticomuscular coherence between C3 and right wrist extensors in infants aged 1-66 weeks corrected age (CA).

Paired EEG and EMG recordings from the forearm extensor muscle and the brain are illustrated in Fig. 2A. 2B and 2C show CMC at different frequencies (B) and the EEG-EMG cumulant density (C). Figures A, B and C show recordings from a single subject (10 week old infant).

The dashed line in Fig. 2B indicates the level of 95% confidence level for the individual coherence estimate. The logarithm of the amount of coherence between EEG and EMG in the 20-40 Hz frequency band is plotted against corrected gestational age for 25 subjects (D). The level of significance is indicated by the horizontal dotted line. The solid line gives the regression for the best fit for the data. The black dots indicate term infants and the white dots indicate preterm infants (<36 weeks of GA). The grey shaded area indicates the developmental ages where FM are observed in typically-developed infants. The mean magnitude of coherence determined using spatial analysis from 13 electrodes in 10 infants is represented by a 2D scalp plot (E) with the C3 electrode occupying the coordinates [0,-3].

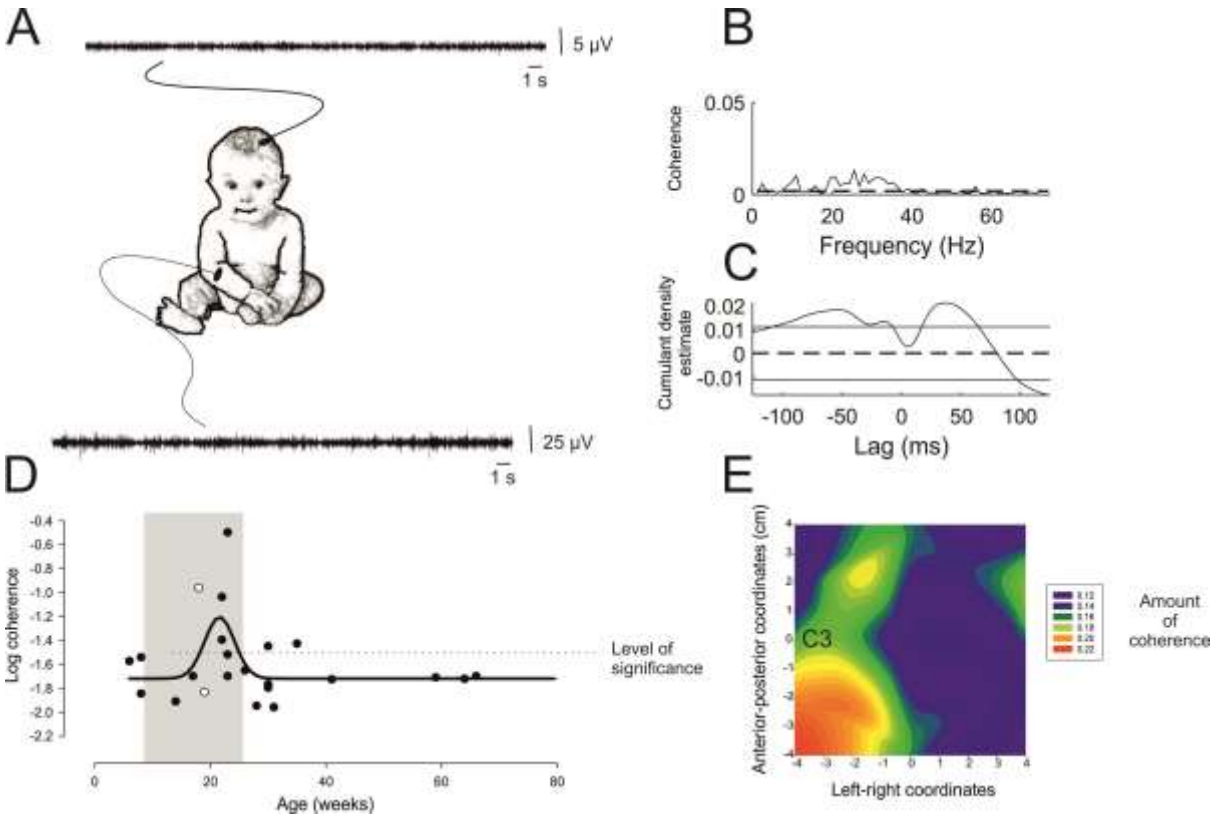

Fig. 3. Coherence between pairs of TA EMG recordings in infants aged 1-66 weeks corrected age (CA).

Fig 3A, Paired EMG-EMG recording from the right Tibialis anterior (TA); two electrodes located proximally and distally over the TA muscle. Threshold 1 and threshold 2 display a discrimination window that captures high amplitude EMG spikes, but diminishes artefacts due to noise. 3B, EMG-EMG coherence and 3C, the corresponding EMG-EMG cumulant density. Figures A, B and C show recording of a 14 weeks old infant.

Dashed line in B and C indicate the level of significance in the individual coherence and cumulant density estimates.

Fig. 3D, for all 48 subjects, the logarithm of the magnitude of EMG-EMG coherence in the frequency range 20-40 Hz is plotted as a function of corrected gestational age. The 95% confidence level for the data is indicated by the horizontal dotted line. The solid line gives the non-linear regression for the best fit for the data. The black dots indicate term infants and the white dots indicate preterm infants (<36 weeks of GA). The grey shaded area indicates the developmental ages where FM are observed in typically-developed infants.

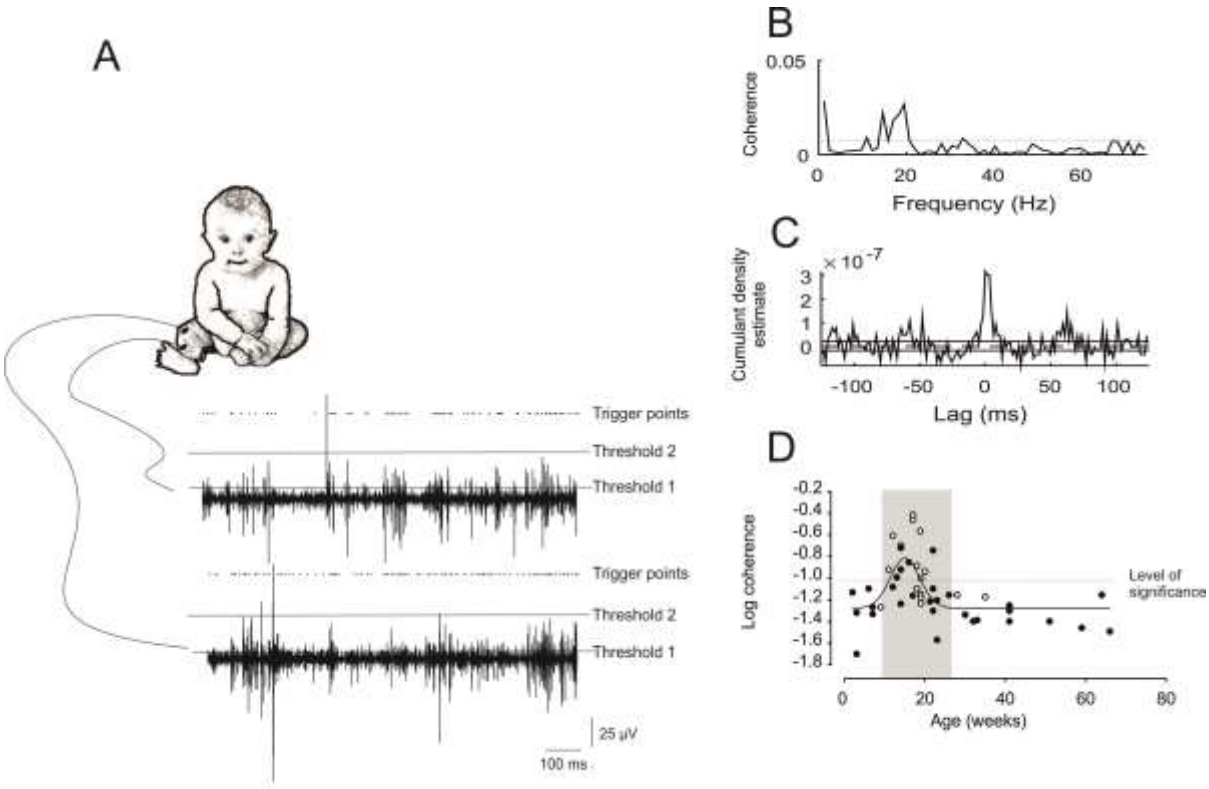

Fig. 4. Pooled estimates of EMG-EMG coherence and cumulant density from Tibialis anterior (TA) muscle related to subject age range.

A, B and C display the EMG-EMG pooled coherence at different frequencies for the three age groups given by the corrected age (CA): 1-8 weeks (A) (8 children), 9-25 weeks (B) (25 children), and >25 weeks (C) (15 children). The dashed lines indicate the 95% confidence levels for the pooled data.

D, E and F show the pooled cumulant for the three age groups. The horizontal lines correspond to the level of 0. Dashed lines indicate the level of significance in the pooled cumulant estimates.

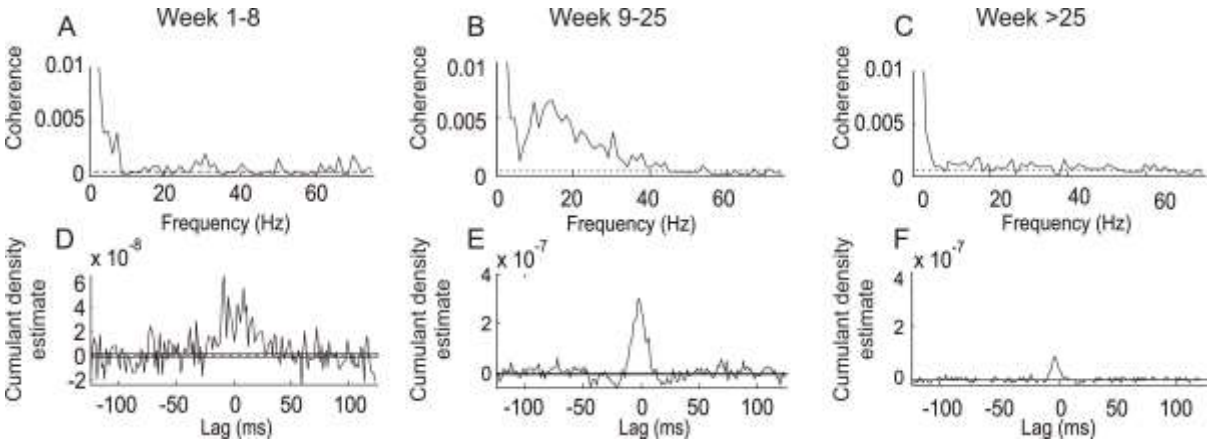

Fig. 5. Correlation between EEG-EMG coherence magnitude and EMG-EMG coherence magnitude

A, The correlation between the log magnitude of CMC and that of Tibialis anterior muscle (TA) EMG-EMG coherence. EEG data taken from Cz electrode. EMG data taken from TA of 59 infants divided into the different age groups; 1-8 weeks are shown in black circles, 9-25 weeks are represented with white circles, and >25 weeks are marked as white triangles. B, The correlation between the log magnitude of CMC between Cz EEG and TA EMG and the log amplitude of EMG-EMG coherence for right wrist extensor muscle in 25 infants (black circles, white circles and white triangles indicate same the age ranges as figure 5A).